Background Document for Meeting of
Advisory Committee for Reproductive Health Drugs
and
Drug Safety and Risk Management Advisory Committee

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of the duration of use for bisphosphonate medications for the treatment and/or prevention of osteoporosis to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 BACKGROUND

1.1 Objective of Meeting

This meeting is being convened to review and discuss the available data regarding the long-term (greater than 3 - 5 years) use of bisphosphonates for the treatment and/or prevention of osteoporosis. In light of recent safety events that appear to potentially be associated with the long-term use of bisphosphonates, FDA believes that it is important to address questions regarding efficacy and the optimal duration of use for bisphosphonates. In this regard, the Division of Reproductive and Urologic Products (DRUP) requested in March, 2010, submission of all available controlled clinical trial data supporting long-term use from all bisphosphonate sponsors with products approved for osteoporosis indications.

The Office of Surveillance and Epidemiology (OSE) will present and review the available data regarding long-term safety issues that have been identified. DRUP will present a review of available long-term efficacy data.

1.2 Issues for Committee Consideration

In January, 2011, as part of a safety labeling change for all of the bisphosphonates approved for the treatment and/or prevention of osteoporosis, the following language was added to the Indications and Usage section of the product labels:

> ***Important Limitations of Use***
> *The safety and effectiveness of [drug] for the treatment of osteoporosis are based on clinical data of [xx] years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis.*

Committee Members will be asked to discuss whether the available data support the long-term use of bisphosphonate medications for the treatment and/or prevention of osteoporosis and whether restricting the duration of use or implementing a drug holiday may be beneficial for patients with osteoporosis who require chronic long-term therapy.

From a safety perspective, the committee will be asked to discuss whether there is sufficient evidence to support an effect of long-term use of bisphosphonates therapy targeted at preventing and/or treating osteoporosis on the risk of developing osteonecrosis of the jaw, atypical fractures or esophageal cancer. Should the committee conclude there is a risk, they will be asked to discuss if there is sufficient evidence of an optimal duration of bisphosphonates use that would minimize these risks.

Committee Members will also be asked to discuss whether the available data support additional labeling changes.

1.3 Osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and increased risk of fracture. Based on NHANES III data, it is estimated that approximately 10 million people in the U.S. have osteoporosis and another 34 million have low bone mass (osteopenia). The goal of therapy is fracture prevention. Fractures, most notably hip fractures, are associated with significant morbidity and mortality. It is estimated that the lifetime risk of a fragility fracture in a postmenopausal woman with osteoporosis is 40-50%. For postmenopausal osteoporosis, there are currently two approved indications for bisphosphonate products:

1. Treatment of osteoporosis in postmenopausal women
2. Prevention of osteoporosis in postmenopausal women

Other approved osteoporosis indications include treatment to increase bone mass in men with osteoporosis and treatment and/or prevention of glucocorticoid-induced osteoporosis.

Osteoporosis is predominantly diagnosed using bone mineral density (BMD) techniques based on the diagnostic criteria set forth by the World Health Organization (WHO) in 1994. However, it has long been recognized that BMD alone is not sufficient to accurately predict fracture risk. Inclusion of other risk factors, most notably age, along with BMD improves facture risk prediction. A risk assessment tool for prediction of osteoporotic fracture (FRAX) was developed by the WHO in 2008. The FRAX algorithms include clinical risk factors that predict an increased risk of fracture (age, sex, prior fragility fracture after age 50 years, history of corticosteroid use [≥ 5mg for more than three months], parental history of hip fracture, rheumatoid arthritis, secondary osteoporosis [e.g., type 1 diabetes, osteogenesis imperfecta in adults, longstanding hyperthyroidism, hypogonadism, premature menopause, chronic malabsorption, and chronic liver disease], current smoker, alcohol use of greater than 2 units daily, and body mass index). The FRAX tool reports fracture risk as the 10-year risk of hip fracture and the 10-year risk of major osteoporotic fracture.

Currently, the National Osteoporosis Foundation recommends treatment be considered for patients who have had an osteoporotic fracture, patients with a BMD T-score of <-2.5 (2.5 standard deviations below the young adult mean), and patients over age 50 years with low bone mass (T-score -1.0 to -2.5) with a risk probability of >3% for hip fracture or >20% for major osteoporotic fracture as obtained using the FRAX algorithm.

Products currently approved in the U.S. for the treatment and/or prevention of postmenopausal osteoporosis are outlined in **Table 1**.

Table 1: Approved Products for Osteoporosis Prevention and/or Treatment

Class	Drug	Route	Dose	Prevention	Treatment
Bisphosphonate	Fosamax (alendronate)	oral	5 mg daily	XX	
		oral	10 mg daily		XX
		oral	35 mg weekly	XX	
		oral	70 mg weekly		XX
	Fosamax PlusD (alendronate)	oral	70 mg/2800IU weekly		XX
		oral	70 mg/5600IU weekly		XX
	Actonel	oral	5 mg daily	XX	XX

Class	Drug	Route	Dose	Prevention	Treatment
	(risedronate)	oral	35 mg weekly	XX	XX
		oral	75 mg 2days/month		XX
		oral	150 mg monthly		XX
	Actonel with Calcium (risedronate)	oral	35 mg once weekly 1250 mg days 2-7	XX	XX
	Atelvia (risedronate-delayed release)	oral	35 mg once weekly		XX
	Boniva (risedronate)	oral	2.5 mg daily	XX	XX
		oral	150 mg monthly	XX	XX
	Boniva (risedronate)	IV	3mg every 3months		XX
	Reclast (zoledronic acid)	IV	5mg yearly		XX
	Reclast (zoledronic acid)	IV	5mg every 2 years	XX	
Estrogen Agonist/Antagonist	Evista (raloxifene)	oral	60 mg daily	XX	XX
PTH analog	Forteo (teriparatide)	SC	20 mcg daily		XX
Calcitonin	Miacalcin (salmon calcitonin, synthetic)	SC	100 IU every other day	XX*	
	Miacalcin (salmon calcitonin, synthetic)	NS	200 IU daily	XX*	
	Fortical (salmon calcitonin, recombinant)	NS	200 IU daily	XX*	
Estrogen and Estrogen/Progestin combination products	Premarin (conjugated estrogen)	oral	0.3 – 1.25 mg daily	XX	
	Premphase (conjugated estrogen, medroxyprogesterone acetate)	oral	0.625 mg daily D1-14 5mg daily D 15-28	XX	
	Prempro (conjugated estrogen, medroxyprogesterone acetate)	oral	0.3/1.5 – 0.625/5 mg daily	XX	
	Climara (estradiol)	trans-dermal	0.025 – 0.1 mg/day, applied once weekly	XX	
	Climara Pro (estradiol, levonorgestrel)	trans-dermal	0.45/0.015 mg/day, applied once weekly	XX	
	Prefest (estradiol, norgestimate)	oral	1 mg estradiol daily for 3 days; alternate with 1/0.09 mg daily for 3 days	XX	
	femhrt (ethinyl estradiol, norethindrone acetate)	oral	2.5/0.5 – 5/1 mg daily	XX	

Class	Drug	Route	Dose	Prevention	Treatment
	Activella (estradiol, norethindrone acetate)	oral	0.5/0.1– 1/0.5 daily	XX	
	Vivelle (estradiol)	trans-dermal	0.025 – 0.1 mg/day, applied twice weekly	XX	
	Alora (estradiol)	trans-dermal	0.025 – 0.1 mg/day, applied twice weekly	XX	
	Menostar (estradiol)	trans-dermal	0.014 mg/day, applied once weekly	XX	
	Vivelle Dot (estradiol)	trans-dermal	0.025 – 0.1 mg/day, applied twice weekly	XX	
RANK ligand inhibitor	Prolia (denosumab)	SC	60 mg every 6 months		XX
* Original Approval based on BMD, not fracture efficacy					

In order to gain approval for the treatment of postmenopausal osteoporosis (PMO), a sponsor must demonstrate that their drug significantly reduces the risk for morphometric vertebral fractures in postmenopausal osteoporotic women during 3 years of treatment.

1.4 Bisphosphonates

Bisphosphonates are pyrophosphate analogs that bind to the hydroxyapatite crystals in bone and inhibit bone resorption through effects on osteoclasts. The first bisphosphonate for the prevention and/or treatment of osteoporosis was approved for the US market in 1995. Since that time, four bisphosphonate molecular entities (alendronate sodium, risedronate sodium, ibandronate sodium, and zoledronic acid) have been approved for treatment and/or prevention of osteoporosis with dosing intervals that vary from daily oral administration to every other year intravenous administration.

The bioavailability of oral bisphosphonates is low (approximately 0.6%). Bisphosphonates are not metabolized. Bisphosphonates that are orally absorbed or intravenously administered either bind to hydroxyapatite in bone or are excreted unchanged into urine. By their binding to hydroxyapatite in bone, bisphosphonates are incorporated into bone's mineral matrix. Release of the drug from the bone mineral matrix requires bone resorption and reduction in bone resorption is the primary mode of action of the drug. Therefore, bisphosphonates have a prolonged residence time in bone. Using modeling performed with alendronate, it is estimated that after 10 years of oral treatment with alendronate 10 mg daily, the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract. This potentially unique aspect of bisphosphonate therapy must be factored into any discussion of the long-term safety and efficacy aspects of bisphosphonates and the question of optimal duration of use.

1.4.1 Bisphosphonate Safety Introduction

During the initial marketing application review as well as in the postmarketing period, safety events for bisphosphonate products have been noted and labeled as Warnings and Precautions.

Disorders of Mineral Metabolism: Bisphosphonate use has been associated with hypocalcemia. Bone is the largest reservoir of calcium in the body with approximately 99% of calcium found in skeletal hydroxyapatite. A small amount of that hydroxyapatite provides the necessary calcium that is freely exchangeable with other bodily fluids and tissues. By binding to skeletal hydroxyapatite and acting to inhibit bone and therefore calcium resorption, bisphosphonates can effectively close off the available calcium exchange from bone. For this reason, pre-existing hypocalcemia is a contraindication and a warning and precaution in all of the bisphosphonate labels.

In the clinical fracture trials for bisphosphonates and other osteoporosis therapies, calcium and vitamin D supplementation is provided as background therapy to all subjects. Therefore, the number of subjects reporting hypocalcemic adverse events in the large clinical trials with bisphosphonates is small. Hypocalcemic tetany attributed to bisphosphonate therapy has been reported rarely in the postmarketing period.

Gastrointestinal disorders: Oral, nitrogen-containing bisphosphonates are well known to cause gastroesophageal adverse reactions attributed to mucosal irritation, particularly of the esophagus. This has been a labeled warning and precaution for all oral bisphosphonates since the initial approval of alendronate in 1995. As more information has become available regarding adverse events of the upper gastrointestinal tract, product labeling has been updated. More recently, concerns have been raised regarding esophageal cancer. These concerns will be discussed further in the long-term safety section of this document.

Musculoskeletal Pain: In the postmarketing period, muscle, joint, and bone pain have been reported with bisphosphonate use. The reported cases have been severe and in some cases incapacitating. There is no clear temporal relationship and the symptoms have been reported to occur within days, months or even years after starting a bisphosphonate. The etiology of the pain is not clear although it does appear to be a separate entity from acute phase reaction symptoms. Warning and precaution language was added to the bisphosphonate labels in 2004.

Renal Adverse Events: Concerns regarding an increased risk of renal toxicity with intravenous bisphosphonates emerged during development of zoledronic acid therapy for oncology indications. The increased risk was dose dependent, with greater incidence in the 8 mg dose group than the 4 mg dose group. The risk of renal toxicity was also improved by an increase in infusion time from 5 minutes to 15 minutes. Therefore, zoledronic acid for oncology indications was approved as a monthly 4 mg intravenous dose to be infused over no less than 15 minutes. A similar dosing algorithm was utilized for the approval of Reclast for the treatment of osteoporosis (5 mg once yearly to be infused over no less than 15 minutes).

In the postmarketing period, adverse events of renal failure requiring dialysis, some with fatal outcome, have been reported with Reclast use. Most cases appear to occur in patients with underlying renal compromise. Renal compromise has not been identified as a safety issue with the other bisphosphonates.

Osteonecrosis of the Jaw: Osteonecrosis of the jaw is a clinical entity that is known to occur in patients exposed to head and neck radiation for the treatment of cancer. Zoledronic acid was approved for oncology indications in 2002. Reports of osteonecrosis of the jaw began

appearing in cancer patients who did not have radiation exposure to the jaw, but were exposed to intravenous bisphosphonates. As further discussed in the long-term safety section of this document, a thorough review of the adverse events was conducted. Osteonecrosis of the jaw was initially labeled in the postmarketing section of the zoledronic acid label in 2004. In 2005, osteonecrosis of the jaw was elevated to a warning and precaution in the intravenous bisphosphonate labels. Because of concerns that the same effects seen with zoledronic acid could also occur with the oral bisphosphonates, osteonecrosis of the jaw warning and precaution language was also added to the oral bisphosphonate product labels in 2005.

Atypical Subtrochanteric and Femoral Diaphyseal Fractures: Subtrochanteric femoral fractures are a subset of proximal femur (or hip) fractures. The subtrochanteric region of the hip is an area of high biomechanical stress due to bending forces combined with torsion from the musculature attached to the femur. Subtrochanteric fractures account for 10 – 30% of hip fractures and are mainly seen in two populations – younger patients with high energy trauma and elderly patients with minor trauma. In the second population of elderly subjects, osteoporosis likely plays a significant role in the etiology of these fractures. The FDA began receiving reports regarding subtrochanteric femoral fractures in patients taking bisphosphonates in 2008. A review of the bisphosphonate clinical trial data was conducted and is outlined in **Table 2**.

Table 2: Hip and Femur Fracture Data from Bisphosphonate Clinical Trials

Drug	Trials (N)	All hip and femur fractures, (subtrochanteric fractures)	Duration of exposure (months)
Fosamax	38	227 (3)	2 - 168
Actonel	22	221 (14)	18 - 48
Boniva	8	60 (0)	N/A
Reclast	7	181 (2)	4 - 9

During review, it became apparent that the features of the subtrochanteric fractures being reported postmarketing were not usual. The clinical trial data available did not allow FDA to investigate whether the subtrochanteric fractures reported in the clinical trials had atypical features. As more information regarding the features associated with these atypical subtrochanteric became available, a search of the literature and the postmarketing adverse events was conducted and is further described and discussed in the long-term safety section of this document. DRUP proceeded with a safety labeling change for all bisphosphonate drugs approved for the treatment and/or prevention of osteoporosis and added a warning and precaution to product labeling in January, 2011, for atypical fractures.

Not all adverse reactions noted in clinical trials or in the postmarketing period require Warning and Precaution language in product labeling. Some are further outlined in the Adverse Reactions sections of the product label and are listed below.

Acute Phase Reaction: Bisphosphonate therapy, mainly intravenous bisphosphonates but also the higher dose weekly and monthly oral products, has been associated with acute phase reaction symptoms. Symptoms suggesting an influenza-like illness occur within three days of the bisphosphonate dose and generally resolve within a week. The symptoms tend to occur early in treatment with the first several doses. Currently, acute phase reaction symptoms are listed as an adverse reaction in product labeling.

Inflammatory Eye Disease: Inflammatory eye disease, such as iritis, uveitis or scleritis, has been reported rarely with bisphosphonate use. In some instances, positive rechallenge occurred, confirming the bisphosphonate as the etiology of the reaction. Currently, inflammatory eye disease is listed as an adverse reaction in product labeling.

Atrial Fibrillation: During the review of zoledronic acid for the treatment of postmenopausal osteoporosis an imbalance in the incidence of serious atrial fibrillation was noted. Based on these concerns FDA requested placebo-controlled clinical trial data from all bisphosphonate sponsors and a thorough review was conducted. The data submitted encompassed 19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients who were followed for 6 months to 3 years. While the zoledronic acid trial showed a statistically significant increase in the rate of serious atrial fibrillation events, across all studies there was no clear association between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation observed. Increasing dose or duration of bisphosphonate therapy was also not associated with an increased rate of atrial fibrillation. Therefore, atrial fibrillation was labeled as an adverse event in the Reclast label and class labeling was not sought.

1.4.2 Bisphosphonate Efficacy

Bisphosphonates have been shown to have robust efficacy in reducing the risk of osteoporotic fragility fractures. In the primary registration trial(s), radiographic evidence of a reduction in vertebral fracture (morphometric vertebral fracture) has been the fracture endpoint of interest. As outlined in **Table 3**, robust fracture reduction efficacy was achieved for all of the bisphosphonate medications. Nonvertebral fracture and hip fracture endpoints, as well as change in bone mineral density, are generally secondary endpoints.

Table 3: Fracture Efficacy with Bisphosphonates – Morphometric Vertebral Fracture

Drug	**N**	**Subjects with Morphometric Vertebral Fracture (%)**		**ARR** (95% CI) (%)	**RRR** (95% CI) (%)
		Drug	**Placebo**		
Fosamax	994	3.2	6.2		49 (5 , 73)
	2027	7.9	15.0	7.1 (5 , 9.2)	47 (32 , 59)
	3066	2.5	4.8	2.3 (1.1 , 3.5)	48 (24 , 65)
Actonel	1374	11.3	16.3	5.0	41
	690	18.1	29.0	10.9	49
Boniva	1952	4.7	9.6	4.9 (2.3 , 7.4)	52 (29 , 68)
Reclast	7736	3.3	10.9	7.6 (6.3 , 9.0)	70 (62 , 76)
ARR = absolute risk reduction; RRR = relative risk reduction					

Bisphosphonates are widely prescribed medications. For the period of 2005 – 2009 in the United States, more than 150 million prescriptions were dispensed in the outpatient setting for the oral bisphosphonates alendronate, risedronate, and ibandronate. The total number of patients who filled a prescription for alendronate, risedronate, and ibandronate are provided in **Table 4**. For the period of 2005 – 2009 in the United States, 5.1-5.7 million patients annually received a dispensed prescription in the outpatient setting for the selected products.

When evaluated by age, 5.1 million patients over the age of 55 years received a prescription for a bisphosphonate in year 2008. We estimate that for every 100 U.S. population, seven patients received a prescription for a bisphosphonate in the outpatient setting.

Table 4: Number of Patients Who Filled a Prescription for an Oral Bisphosphonate

	2005	2006	2007	2008	2009
Grand Total	5,083,730	5,640,382	5,479,241	5,696,298	5,185,240
Age 55+ on bisphosphonate	4,301,360	4,885,301	4,808,291	5,061,588	4,542,988
Age 55+ (U.S. Census)	67,085,690	68,822,246	70,668,349	72,555,897	unavailable
Prevalance per 100 US population Age 55+	6.41	7.10	6.80	6.98	
Female patients age 55+ on bisphosphonate	3,978,997	4,523,151	4,446,305	4,668,453	4,183,457
Age 55+ female (U.S. Census)	37,077,356	37,955,188	38,887,117	39,840,455	unavailable
Prevalance per 100 US population Age 55+ (female)	11	12	11	12	

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts. Source: SDI Total Patient Tracker. Data Extracted 4/2010.

2 Bisphosphonate Long-Term Use: Safety

2.1 Overview of Long-Term Safety Issues

The safety of long-term bisphosphonate therapy is a topic of much debate as adverse events continue to be reported and published. Safety concerns with potentially severe clinical outcomes that have been reported with long-term use of bisphosphonates include atypical subtrochanteric and femoral fractures, osteonecrosis of the jaw, and esophageal cancer. This safety review will focus on data reported to the FDA Adverse Event Reporting System and the epidemiological evidence available for these three outcomes.

2.2 Review and Utility of Postmarket Adverse Events Reports to FDA

This section summarizes FDA's use of postmarketing data concerning atypical femoral fractures, osteonecrosis of the jaw (ONJ), and esophageal cancer following bisphosphonate exposure for the treatment and prevention of osteoporosis.

FDA uses a computerized information database (Adverse Event Reporting System or AERS) for post-marketing safety surveillance of drug and therapeutic biologic products. This database stores individual safety reports concerning suspected adverse drug reactions. Analysts in CDER's Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance II (DPV II) performed AERS-based assessments for the adverse outcomes noted above but were unable to characterize the relationship of these adverse event outcomes to bisphosphonate exposure due to limitations of the database. First, there is no certainty that a reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. A reported event may actually have been due to an underlying disease process, a different drug, another coincidental factor, or combination of factors. The AERS database includes suspected events; physicians are encouraged to report suspected events.

Further, FDA does not receive all adverse event reports that occur with a product. People experience adverse events and the events are never reported. Many other factors can influence whether or not an event will be reported, such as the length of time a drug is marketed, the market share, size and sophistication of the sales force, and awareness bias (i.e., publicity, regulatory action, or educational campaign about a drug and adverse event combination). The vast majority of reports to AERS, which includes both foreign and domestic sources, are voluntarily submitted directly to the system by healthcare practitioners and consumers or to product manufacturers who have regulatory requirements for submitting reports to AERS.

Therefore, AERS data cannot be used to calculate the incidence or occurrence rates of an adverse event in the population, which are necessary to make the most accurate risk assessments for specific adverse events. The actual number of adverse events cannot be accurately determined because reporting is voluntary and because the number of patients actually taking the drug is not always known. In addition, to determine if a drug caused an adverse event, the report must be evaluated by a trained professional who conducts an evaluation of the cases to interpret the information; however, in most instances it is not possible to clearly determine whether a causal relationship exists between drug exposure and the adverse event reported. In addition AERS data generally can not be used to compare drug products or to determine the safety of different drug dosages.

Specific limitations of AERS data in relation to the long-term safety issues of concern with bisphosphonates include the fact that duration of therapy is often omitted from reports. Additionally, reporters may be less likely to attribute causality, and subsequently report, adverse events that occur long after initiation of therapy.

Overall, DPV II was unable to characterize the relationship of the adverse event outcomes of interest to bisphosphonate exposure primarily due to inherent limitations of spontaneously reported safety information made more problematic by uncertain case definition criteria, most notably for atypical femoral fractures and ONJ.

Summary findings of DPV II's AERS assessments are detailed below.

2.2.1 Osteonecrosis of the Jaw

OSE initially assessed ONJ with bisphosphonate use (for oncology indications) in 2003 (intravenous formulations) and 2004 (oral formulations) and recommended this event be labeled [see Chang Reviews in Appendices 1 and 2]. Following an Oncologic Drugs Advisory Committee (ODAC) meeting on March 4, 2005, FDA received additional AERS cases of ONJ in women using bisphosphonates for osteoporosis [see Pamer Review in Appendix 3]. Prior to 2007, a widely accepted clinical definition of osteonecrosis of the jaw did not exist. In 2007 an American Association of Oral and Maxillofacial Surgeons (AAOMS) Task Force published a definition for bisphosphonate-related ONJ (BRONJ) requiring the following clinical characteristics:[2]

[2] Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. J Oral Maxillofac Surg. 2007;65(3):369-76.

1. Current or previous treatment with a bisphosphonate;
2. Exposed bone in the maxillofacial region that has persisted for more than eight weeks; and
3. No history of radiation therapy to the jaws.

The Task Force report states that intravenous bisphosphonate use in patients with malignancy is a major risk factor for bisphosphonate-related ONJ. The Task Force report also states that patients receiving oral bisphosphonates are at a lower risk for bisphosphonate-related ONJ than cancer patients receiving monthly intravenous bisphosphonate treatments.

In March 2010, the Medical Dictionary for Regulatory Activities (MedDRA) preferred term "osteonecrosis of jaw" was established. Prior to March 2010, AERS reports of ONJ were difficult to identify due to the lack of specificity in the adverse event coding dictionary. Additionally, AERS reports of possible ONJ were not the subject of a formal review by safety analysts as cursory inspection of the reports showed a lack of clinical detail satisfying the AAOMS case definition above. FDA determined that AERS data were not sufficient to characterize ONJ and that epidemiological studies were necessary to help determine the incidence rate.

2.2.2 Atypical Femoral Fractures

In 2005 the occurrence of atypical femoral fractures with bisphosphonate use was first described[3] and in 2008 FDA opened a Safety Issue Application (SIA) to track this safety issue. However, prior to 2010 a widely accepted clinical definition of atypical femoral fracture did not exist. In November 2010, the American Society for Bone and Mineral Research (ASBMR) Task Force published a proposed case definition with diagnostic criteria for atypical femoral fractures with bisphosphonate exposure, presented in Table 2.1 below. The most noteworthy major feature is that designation of atypical femoral fractures requires no or minimal trauma.[4]

Based on a draft ASBMR definition, DPV II broadly searched AERS in March 2010 for cases of atypical fracture with all marketed bisphosphonates (alendronate, etidronate, ibandronate, pamidronate, risedronate, tiludronate, zoledronate). At that time, DPV II found 1623 AERS reports using various search terms (e.g., "femur fracture," "lower limb fracture," "pathologic fracture") related to femoral fracture and forwarded them to the Division of Urologic and Reproductive Products (DRUP) for case review and adjudication. After narrowing the search using specific terms from the ASBMR draft case definition, DRUP identified 126 cases containing various clinical and radiographic features of interest cited as being associated with bisphosphonate-related atypical subtrochanteric fractures. Nonetheless, DRUP was unable to reach any firm exposure-event conclusions because many reports did not contain enough data specific for the clinical features noted in the ASBMR draft case definition. Subsequently, FDA internally determined that a large observational study or

[3] Odvina C, Zerwekh J, Rao S, et al. Severely suppressed bone turnover: A potential complication of alendronate therapy. J Clin Endocrinol Metab 2005; 90(3): 1294-1301.

[4] Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010; Vol 25 (Issue 11):2267–2294.

clinical trial with specific diagnostic criteria would be a more appropriate method to evaluate this safety issue.

2.2.3 Esophageal Cancer

In January 2009 a publication in the New England Journal of Medicine using AERS postmarket data described 23 patients in the United States who received a diagnosis of esophageal cancer while using alendronate. The author noted a major limitation of AERS data is underreporting and that the extent of reporting is variable. Consequently, reliable incidence rates of esophageal cancer among users of oral bisphosphonates cannot be calculated from these reports and compared with U.S. cancer rates or those obtained from other sources.[5,6] Another significant limitation of AERS data was the absence of histologic analysis in most of the reports (65%) which is essential for evaluation given the biological plausibility of developing esophageal cancer following bisphosphonate exposure. Knowledge of the histologic subtype helps to distinguish Barrett's esophagus (i.e., adenocarcinoma) from other cancer etiologies such as tobacco abuse, etc.

More recently, epidemiologic studies have been published on the association of esophageal cancer and oral bisphosphonates with conflicting results.[7,8] These studies are described more fully in the Section 2.3.3.

2.3 Epidemiological Evidence

This section summarizes FDA's review of epidemiological studies concerning osteonecrosis of the jaw, atypical subtrochanteric and femoral fractures, and esophageal cancer with an emphasis on long-term duration of use of bisphosphonates for the prevention and treatment of osteoporosis.

2.3.1 Osteonecrosis of the Jaw

Because it is a relatively rare disease, few studies have been able to evaluate the potential association between bisphosphonates and osteonecrosis of the jaw (ONJ). The incidence of ONJ among the general population is unknown but is estimated to be in the range of 1-5% among cancer patients who receive intravenous (IV) bisphosphonates for management of skeletal lesions.[9] Three observational studies identified a 4 to 5-fold increased risk of an ONJ disease-related procedure or diagnosis associated with IV bisphosphonate use for cancer

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[5] Wysowski DK. Reports of Esophageal Cancer with Oral Bisphosphonate Use. N Engl J Med, January 1, 2009. 360: 1

[6] Wysowski DK. More on Reports of Esophageal Cancer with Oral Bisphosphonate Use. N Engl J Med, April 23, 2009. 360: 17

[7] Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA 2010;304:657-663 (1).

[8] Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of the oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ 2010;341:doi:10.1136/bmj.c4444 (2).

[9] Lo JC et al. Predicting Risk of Osteonecrosis of the Jaw with Oral Bisphosphonate Exposure (PROBE) Investigators. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg. 2010 Feb;68(2):243-53.

indications.[10,11,12] The focus of this background document, however, is the use of bisphosphonates for the prevention and treatment of osteoporosis.

To obtain safety information on oral bisphosphonates, FDA collaborated with Kaiser Permanente of Northern California (KPNC) in 2006 to conduct a pharmacoepidemiologic study with the purpose of quantifying and characterizing the risk of ONJ with oral bisphosphonates [see McCloskey Review in Appendix 4]. The "Predicting Risk of Osteonecrosis with Bisphosphonate Exposure" (PROBE) study was a cross-sectional study[9] conducted to determine the prevalence of ONJ among patients using oral bisphosphonates (Phase I) and to examine other possible risk factors and effect modifiers for the development of ONJ among patients with oral bisphosphonate exposure (Phase II).

A dental symptom survey was mailed to 13,946 adult members of KPNC aged 21 to 90 years in 2007 with any oral bisphosphonate prescriptions (alendronate, ibandronate, and risedronate) for at least one year. The survey inquired about dental symptoms including moderate periodontal disease, history of gingival/palatal sores, exposed bone/ONJ, history of complication after invasive dental procedure and persistent/current symptoms of gums, teeth or jaw in year prior to survey. Responses were received from 8572 (62%) patients who were surveyed. Responders who reported oral or dental symptoms (n=2159) were invited for a screening examination or verification of oral health status through dental record review. All highly suspicious cases were then evaluated by an oral surgeon and adjudicated as ONJ, ONJ-like findings, or Stage 0 disease using the following definitions (**Table 5**)[13].

[10] Zavras AI, Zhu S. Bisphosphonates are associated with increased risk for jaw surgery in medical claims data: is it osteonecrosis? J Oral Maxillofac Surg. 2006 Jun;64(6):917-23.

[11] Wilkinson GS, *et al*. "Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis." Journal of the National Cancer Institute 99.13 (2007):1016-1024.

[12] Cartsos VM, Zhu S, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. J Am Dent Assoc. 2008 Jan;139(1):23-30

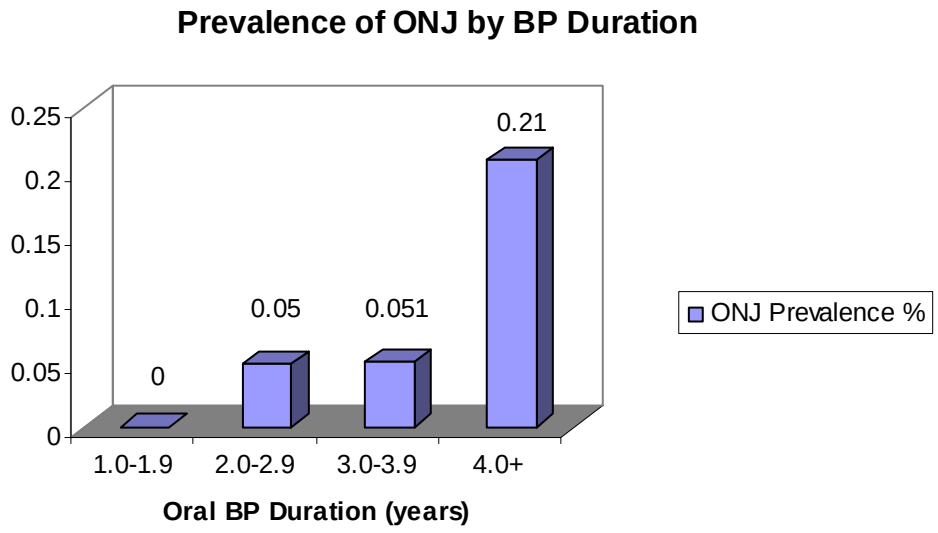
[13] ONJ (including Stage 0) are based on the American Association of Oral and Maxillofacial Surgeons (AAOMS) Position Paper published in 2009.

Table 5: ONJ Definitions

Outcome	Definition
Osteonecrosis of the Jaw (ONJ)	1. Current or previous treatment with a bisphosphonate 2. Exposed bone in the maxillofacial region persisting >8 weeks 3. No history of radiation treatment to the jaws
ONJ-like Findings	1. Current or previous treatment with a bisphosphonate 2. Findings concerning for ONJ but not meeting the case definition (<8 weeks exposed bone, purulent osteomyelitis)
Stage 0 BRONJ	Based on AAOMS definition of Stage 0 BRONJ 1. Current or previous treatment with a bisphosphonate 2. No clinical evidence of exposed or necrotic bone 3. Concerning radiographic findings, including dense sclerotic bone, thickening of the lamina dura; persistence of unremodeled bone in extraction sockets.

The prevalence of ONJ (excluding Stage 0 disease) among survey respondents was 0.1% (95% confidence interval 0.05% to 0.2%) or a frequency of 28 (95% CI 14 to 53) per 100,000 person-years of oral bisphosphonate treatment (**Figure 1**). All cases were Stage 1 or 2. About 78% (n=7) of the ONJ patients were exposed to oral bisphosphonates for 4 or more years with a median duration of 4.4 years; the minimum number of years exposed was 2.6. The median duration of exposure among those without ONJ was 3.5 years.

Figure 1: Prevalence of ONJ by Bisphosphonate Duration - PROBE Study 2007



When adjusted for age and presence of rheumatoid arthritis a four-fold increased odds of ONJ was observed among patients who used bisphosphonates for 4 or more years compared to those who used the medication for less than 4 years [OR=4.45, 95%CI (0.92 to 21.54)].

An additional 10 cases of Stage 0 BRONJ and 10 cases with ONJ-like findings were identified. Analyses were done using a composite outcome of ONJ, ONJ-like findings, and

Stage 0 disease. Again patients with longer duration of use (4 years or greater) had an increased odds of disease [OR=2.11, 95%CI (1 to 4.46)].

Conclusion

The data are suggestive of an increased prevalence of ONJ and ONJ-like findings with increased duration of exposure to oral bisphosphonates, with the highest prevalence occurring at 4 or more years of use. These results should be interpreted with caution as this study is a prevalence study and was not designed to determine whether the outcome occurred before or after initiation of therapy. Causation of ONJ by oral bisphosphonates would need to be confirmed with longitudinal studies with appropriate comparator groups, designed to account for other potential confounding factors. This has proven difficult given the rarity of ONJ.

2.3.2 Atypical Fractures

A number of case series and case reports have been published since 2005 describing unusual femoral fractures which were identified in patients taking bisphosphonate drug products.[14] In response, several epidemiologic studies have been conducted to evaluate this potential association between bisphosphonates and these unusual fractures which have been designated as atypical. However, the definition of atypical femoral fracture has been inconsistent across these studies and reports. Some studies classify a femoral fracture as atypical based on whether the fracture was the result of a non-traumatic incident such as a fall from standing height or less. Others have used specific radiographic features such as transverse or oblique fracture, lateral cortical thickening and/or beaking. Although there has been variation in the definition, atypical femoral fractures are always characterized in part by the location of the fracture. Typical osteoporotic fractures of the hip usually involve the femoral neck or intertrochanteric region. On the other hand, *atypical femoral fractures* exclude those occurring in these typical regions, and are characterized by occurrence in the subtrochanteric region and in the femoral shaft or diaphysis. Inconsistent use of the term 'atypical fractures' makes it difficult to estimate the background incidence of these fractures. One study by Nieves *et al.* estimated the national hospital discharge rate for closed atypical femoral fractures between the year 1996 and 2006 to be approximately 20 per 100,000 women compared to about 500 hip fractures per 100,000 women.[15] These fractures can be associated with significant morbidity and mortality, with one study showing a mortality rate of 14% at 12 months.

In 2010 the American Society for Bone and Mineral Research (ASBMR) appointed a task force to develop a case definition for atypical femoral fracture. The derived definition excluded fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors and peri-prosthetic fractures. Characteristics identified as required for a fracture to be designated as

[14] Shane E, American Society for Bone and Mineral Research, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010 Nov;25(11):2267-94.

[15] Nieves JW, Bilezikian JP, Lane JM, Einhorn TA, Wang Y, Steinbuch M, Cosman F. Fragility fractures of the hip and femur: incidence and patient characteristics. Osteoporos Int. 2010 Mar;21(3):399-408.

atypical were termed 'Major Features', while other 'Minor Features' were identified as sometimes being associated with but not required for a diagnosis (**Table 6**).

Table 6: Major and Minor Features of Atypical Fractures

Major Features

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Non-comminuted
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex

Minor Features

- Localized periosteal reaction of the lateral cortex (beaking or flaring)
- Generalized increase in cortical thickness of the diaphysis
- Prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral fractures and symptoms
- Delayed healing
- Comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia)
- Use of pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors)

†Adapted from Shane *et al*. 2010

To inform the FDA's understanding of atypical fracture and to guide further review of this issue, a comprehensive PubMed search was conducted utilizing the following search terms: alendronate, pamidronate, ibandronate, risedronate, zoledronic acid, femoral fracture, subtrochanteric fracture. Longitudinal observational studies and randomized clinical trials (RCT) published between 1995 and April 2010 were included in the review [see Moeny Review in Appendix 5]. For the purposes of this Advisory Committee Meeting, the literature search was updated to include studies published up until July 2011. Ten articles (9 observational studies and 1 secondary analysis of 3 RCTs) were included in this final review (**Table 7**).

The observational studies have mostly shown an increased risk of atypical fractures among bisphosphonate users compared to non-users although the incidence rates are very low in both groups. The evidence with regard to long-term exposure is conflicting.

One study using Danish National Registry data assembled a cohort of patients who had suffered fractures in places other than the hip.[16] Within this population, two exposure groups were identified: exposed to bisphosphonates (alendronate) or unexposed to bisphosphonates. The rates of atypical femoral fracture and hip fracture were compared between the two

[16] Abrahamsen B, Eiken P, Eastell R. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res. 2009 Jun;24(6):1095-102.

exposure groups. The authors observed increased rates of atypical femoral fracture adjusted for age, sex and baseline comorbidity in alendronate users compared to non-users, although this difference was not statistically significant [Hazard Ratio(HR) = 1.46; 95% confidence interval (CI) 0.91-2.35, p=0.12]. Of interest, they also observed that the proportion of fractures that were atypical femoral fractures was similar in the exposed and unexposed groups (10% vs. 12.5%). Among a subset of patients using alendronate for more than 6 years and with >80% adherence, the risk of atypical fractures was slightly lower than that observed for the entire exposed cohort [HR= 1.37 (0.22-8.62)], although not statistically significant. The same authors in a different study observed that the effect was modified by gender with men having higher risks of atypical fractures than women.[17] They also confirmed their previous findings regarding a lack of duration effect [Incidence Rate (IR) per 100,000 person-years at 0.2, 1.1, 3.7 and 8.7 years = 56.7, 27.9, 29.7, and 26 respectively, p=0.22]. Another Danish registry study had similar findings of higher rates of atypical fractures among patients using bisphosphonates compared to untreated controls [HR(95% CI) = 2.41(1.78-3.27); 1.9(1.62-2.36); 20(1.94-205) for alendronate, etidronate, and clodronate respectively].[18] However, they also observed increased rates prior to initiating bisphosphonates [OR (95%CI) = 2.36(2.05-2.72); 3.05(2.59-3.58); 1.08(1.14-103)]. This study found no association with dose or duration of use. These data are consistent with a secondary analysis conducted by Black *et al.* of three randomized clinical trials, which also found no increased risk of atypical fractures with use of alendronate or zoledronic acid.[19]

On the contrary, five observational studies [Guisti 2010, Lenart 2010, Park-Wyllie 2010, Schilcher 2011, and Wang 2011] each concluded that bisphosphonate use was associated with an increased risk of atypical femoral fractures. Studies using definitions similar to that recommended by the ASBMR Task Force showed the highest increases in atypical fracture among bisphosphonate users. Lenart et al observed that patients with subtrochanteric and femoral shaft fractures that showed cortical thickening and beaking on radiographs were 15 times more likely to have used bisphosphonates compared to patients whose radiographs did not show these features [OR=15.33 (3.06-76.90)].[20] Another case-control study observed a 17-fold increase in bisphosphonate use among patients with atypical femoral fractures defined using features from the ASBMR Task Force recommendation, when compared to patients with other subtrochanteric and femoral shaft fractures [OR=17(2.6-113.3)].[21] However, this study also found that atypical femoral fractures occur at similar rates in bisphosphonate users and non-users. The third study to use an ASBMR-like definition of atypical femoral fracture observed a 33-fold increase in bisphosphonate use among patients

[17] Abrahamsen B, Eiken P, Eastell R. Cumulative alendronate dose and the long-term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab. 2010 Dec;95(12):5258-65

[18] Vestergaard P, Schwartz F, Rejnmark L, Mosekilde L. Risk of femoral shaft and subtrochanteric fractures among users of bisphosphonates and raloxifene. Osteoporos Int. 2011 Mar;22(3):993-1001

[19] Black DM, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med. 2010 May 13;362(19):1761-71.

[20] Lenart BA, et al. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. Osteoporos Int. 2009 Aug;20(8):1353-62

[21] Giusti A, et al. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. Bone. 2011 May 1;48(5):966-71

with atypical femoral fractures compared to patients with other subtrochanteric and femoral shaft fractures not fitting the criteria [OR=33.3 (14.3-77.8)]. There was an even larger increased risk among patients who had used bisphosphonates for more than 2 years [OR=51.1(20.3-128.2)].[22] The risk estimate was much smaller in another positive study that defined atypical fractures using ICD-9 codes for subtrochanteric and femoral shaft fractures.[23] This study was the only other study to find an increase in risk with increased duration of use, observing a 3-fold increased odds of bisphosphonate use greater than or equal to 5 years among patients with subtrochanteric and femoral shaft fractures compared to patients without fractures [OR=2.74(1.25-6.02)].

The conflicting results observed across studies is likely due in large part to inconsistent case definitions. Earlier studies tended to not find an association while more recent data support some association between bisphosphonate use and atypical fractures. Studies using a case definition similar to that recommended by the ASBMR Task Force show stronger associations with bisphosphonate use. One of those studies found a significant increase with 2 or more years of use, further strengthening the case for an association between bisphosphonates and fractures with ASBMR case definition radiographic features. The clinical significance of these radiographic findings has yet to be determined. The overall evidence with regard to a duration or cumulative dose response is conflicting, which may also be a result of inconsistent case definitions across studies. Among studies that did find a cumulative dose response, there is disagreement as to how much cumulative use is harmful, with one study finding an increased risk after 5 or more years, while another study found an effect after only 2 or more years. Of those studies that did report overall duration of bisphosphonate use among atypical fracture cases, the average number of years of bisphosphonate use ranged from 2 to 7 years.

Confounding by indication could contribute to the increased risk observed, as indicated in studies that showed an increase in risk of atypical femoral fracture even before initiating bisphosphonate therapy. Using a sample of the general population as comparators could overestimate risk especially if the pathogenesis of atypical femoral fracture is more related to the disease process of osteoporosis than to use of bisphosphonates. Residual confounding due to unmeasured confounders is also possible even in those studies that used cohorts of osteoporotic patients.

Conclusion

Atypical subtrochanteric and femoral shaft fractures occur at very low rates that pale in comparison to typical hip fractures, and may not be specific to bisphosphonate users. Atypical fractures, as defined by the ASBMR Task Force appear to have a strong association with bisphosphonates, although causality has not been determined. Finally, there is no agreement on the extent to which cumulative use of bisphosphonates increases the risk of atypical fractures.

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[22] Schilcher J, Michaëlsson K, Aspenberg P. Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med. 2011 May 5;364(18):1728-37

[23] Park-Wyllie LY, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. JAMA. 2011 Feb 23;305(8):783-9.

Table 7: Atypical Fracture Literature Summary Table

Author (Year)	Study Design	Atypical Fracture Definition	Risk	Duration of Use Among AFx Cases
Abrahamsen (2009)	Cohort Alendronate users w/ h/o fx vs. unexposed (to BP) w/ h/o fx	Low energy ST and DF fx	AFx HR=1.46 (0.91-2.35) HipFx HR=(1.45 (1.21-1.74) BP >6 yr: HR=1.37 (0.22-8.62)	Not reported
Abrahamsen (2010)	Cohort Alendronate users vs. untreated controls	ST or DF fx	HR=1.88 (1.62-2.17) No duration effect IR per 10,000 p-y at 0.2, 1.1, 3.7, and 8.7 years of BP use = 56.7 , 27.9, 29.7, and 26 respectively (trend test p=0.22)	Mean time to fracture = 2.6 years 6.6 yrs among subgroup who began therapy between 1996 and 1999
Black (2010)	2^{o} analysis of 3 RCTs	ST and DF fx identified by radiographs or radiology reports	RCT1: HR=1.03 (0.06-16.43) RCT 2: HR=1.5 (0.25-9) RCT 2: HR=1.33 (0.12 – 14.67)	Mean time to fracture = 3 years (based on avg number of days from randomization to fracture
Giusti (2010)	Case-Control compare current BP among AFx vs ST/FS	Atypical: Transverse or short oblique, non-comminuted ST/FS fx in area of thickened cortices with unicortical beaking	OR=17(2.55-113.26)	Range 3-5 years
Kim (2011) A, Ri, E	Cohort Cohort of BP users vs Cohort of raloxifene/ calcitonin users	ST or DF fx identified using ICD-9 codes for hospital discharge diagnosis.	BP users IR per 1000 p-y=1.46(1.11-1.88) Raloxifene/Calcitonin Users IR=1.43(1.06-1.89) HR=1.03 (0.70-1.52) BP >5yrs: HR=2.02(0.41-10)	Not reported
Lenart (2009)	Case-Control Compare BP use b/w Afx and Hip Fx	ST/FS fracture with cortical thickening and beaking of the cortex	BP Use OR= 4.44 (1.77-11.35) OR of X-ray patterns OR, 15.33 [95% CI 3.06-76.90]; P < 0.001	Mean 7.3 yrs
Park-Wyllie (2011)	Nested Case-Control	Low energy ST/FS fx leading to hospitalization (ICD-10 codes)	BP ≥5yrs vs. <100 days: OR=2.74(1.25-6.02) BP 3 to 5 yrs vs. <100 days: OR=1.59(0.80-3.15)	Median 4 years
Schilcher (2011) A, Ri, E, I (all oral)	Nested Case-Control Compare BP use b/w AFx and ST/FS fx w/o xray xteristics	Stress fx, transverse on lateral side w/o fragments, w/ or w/o cortical thickening	OR=33.3(14.3-77.8) OR[<1yr]=9.8(1.9-49.9) OR[1-1.9yr]= 7.1(1.6-30.7) OR[>2yr]=51.1(20.3-128.2)	3yrs
Vestergaard (2011)	Cohort BPs, raloxifene, strontium & PTH) vs. matched control from gen popn	ST and FS fx	HR(95% CI) = 2.41(1.78-3.27); 1.9(1.62-2.36); 20(1.94-205) for alendronate, etidronate, and clodronate respectively No dose relationship No duration relationship (<2 yrs, >2yrs, >5yrs)	Not reported
Wang (2011)	Ecologic Trend Analysis 1996-2007(national trend in exposure vs. trend in outcome)	ST fragility fracture: hospitalization with a primary diagnosis ICD-9 code for closed ST fracture	31.2% increase prevalence in ST fx; p<0.05 In women: Increase in proportion of ST by 2.1% Increase in BP use by 14.9% Increase in BP use preceded increase in proportion of ST fx	Not reported

ST- subtrochanteric, DF – diaphyseal femur, Fx – fracture, AFx – atypical fracture, HR – hazard ratio, FS – femoral shaft, BP – bisphosphonate, RCT – randomized controlled trials

2.3.3 Esophageal Cancer

Esophagitis and esophageal ulcer are well-recognized adverse events associated with use of oral bisphosphonates. More recently, reports of esophageal cancer in patients exposed to oral bisphosphonates have been the topic of much debate.

Two large observational studies were published in 2010 on the association between oral bisphosphonates and esophageal cancer and were reviewed by the Division of Epidemiology and the Division of Reproductive and Urologic Products [See Reviews by Staffa and Voss in Appendix 6 and 7, respectively]. Both studies utilized the United Kingdom's General Practice Research Database (GPRD) during similar time periods (1995 to 2005 and 1996 to 2006). The study by Cardwell et al[24] used a retrospective cohort design and compared exposed oral bisphosphonate users to a control cohort, while Green et al[25] used a nested case-control design. The cohort study reported no difference in the risk of esophageal cancer between the cohorts for any bisphosphonate use [HR=1.07 (0.77-1.49) adjusted for BMI, alcohol, smoking, hormone replacement prescription, NSAID, Barrett esophagus, GERD and H2 receptor antagonist use]. There was no difference in risk of esophageal cancer by duration of bisphosphonate use. On the other hand the case-control study reported an increased incidence of esophageal cancer in a small proportion of bisphosphonate users with one or more previous prescriptions for oral bisphosphonates compared to those with no prescriptions [Relative Risk (RR) = 1.30 (1.02-1.66)]. Stratified analyses showed that the risk of esophageal cancer was significantly higher for patients with 10 or more prescriptions [RR=1.93 (1.37-2.70)] than for patients with one to nine prescriptions [RR=0.93 (0.66-1.31)] and for use over 3 years compared with no prescription [RR=2.24 (1.47-3.43)]. Two other smaller studies, one utilizing data from the Danish Registry[26] and another using United States Medicare claims data and SEER data[27] also failed to find an association.

Differing results from the same database (GPRD) and time period could be explained by difference in study designs. The case control study had a longer overall observation period with a mean of 7.5 years, although mean follow-up among bisphosphonate users was similar in the two studies (4.5 years in the cohort study and 4.6 years in the case-control study). The cohort study could be limited by lack of power to detect a difference, especially with a rare disease such as esophageal cancer. Case definitions differed across the two studies and may not be comparable. In their statistical model, the authors of the cohort study adjusted for covariates such as Barrett's esophagus and gastroesophageal reflux disease that may be in the causal pathway of esophageal cancer; this could mask any association that may otherwise have been observed if they were reported separately.

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[24] Cardwell CR, et al. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA. 2010 Aug 11;304(6):657-63.

[25] Green J, et al. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ. 2010 Sep 1;341:c4444

[26] Abrahamsen B, Eiken P, Eastell R. More on reports of esophageal cancer with oral bisphosphonate use. N Engl J Med. 2009 Apr 23;360(17):1789.

[27] Solomon DH, Patrick A, Brookhart MA. More on reports of esophageal cancer with oral bisphosphonate use. N Engl J Med. 2009 Apr 23;360(17):1789-90.

Because of the limitations of these studies it is impossible to designate any one of these studies as the conclusive study providing the answers to this safety issue. A definitive study would address the effect of bisphosphonate use on esophageal cancer development and would assess bisphosphonate use/misuse, its relationship to the development of GERD and Barrett's, and its subsequent contribution to esophageal cancer if any. However this may prove difficult to carry out given the low prevalence of esophageal cancer in women. Long-term follow up of new users of bisphosphonates without a diagnosis of GERD would be pertinent to the success of such a study.

Conclusion
The available evidence regarding the possible association between oral bisphosphonates and esophageal cancer is inconclusive. Consequently, no conclusion can be reached as to whether long-term use of bisphosphonates is associated with esophageal cancer.

2.4 Overall Summary of Long-Term Safety Issues

The safety of long-term bisphosphonate therapy continues to be unclear as study results are conflicting as to whether or not ONJ, atypical femoral fractures or esophageal cancer are associated with use of bisphosphonates for the prevention and treatment of osteoporosis. The epidemiologic evidence concerning ONJ is suggestive of an increased prevalence of ONJ and ONJ-like findings with increased duration of exposure to oral bisphosphonates, with the highest prevalence observed at 4 or more years of use. However these results would need to be confirmed by additional larger studies. Atypical fractures with radiographic features defined by the ASBMR Task Force appear to have a strong association with bisphosphonates but there is no current consensus on the extent to which cumulative use of bisphosphonates increases the risk of this rare type of fracture. Finally, no definitive evidence is available to support an association between esophageal cancer and long-term use of bisphosphonates.

3 Bisphosphonate Long-Term Use: Efficacy

3.1 Study Design Overview

Because of concerns regarding the long-term safety signals, it is important to review the available data supporting the long-term efficacy of bisphosphonates in the treatment and/or prevention of osteoporosis. The Division reviewed the available long-term data (>3 years duration) for those bisphosphonates approved for the treatment of osteoporosis: Fosamax (alendronate), Actonel (risedronate), Boniva (ibandronate), and Reclast (zoledronic acid). Four studies met the following criteria: duration greater than 3 years, systematic collection of data, inclusion of a useful comparator group, and the capture of clinical fractures as well as morphometric vertebral fractures.

An overview of the available data is shown in **Table 8** with data ranging from 5 to 11 years of continued exposure. Studies for each drug product were designed differently with variable entry criteria, DXA skeletal sites, fracture monitoring system, and treatment duration. The Fosamax and Reclast study designs were the most similar and incorporated randomized withdrawal phases. Continuous Actonel exposure data exist up to seven years with a placebo-control comparison through year 5. Actonel data also included a prospectively planned one-

year drug holiday in year 8 for a small subset of subjects (n=32). The Boniva pivotal fracture trial was 3 years in duration but did not include an extension period. The two long-term Boniva trials, shown in **Table 8**, had BMD endpoints rather than fracture endpoints, did not have any non-ibandronate groups for comparison, and did not capture all fracture events reliably. Based on these limitations, the Boniva data were not included in any of the exploratory analyses.

Table 8: Long-term Bisphosphonate Studies

Timeline (years)									
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**
Fosamax									
FIT (Years 0-4)					**FLEX (Years 0-5)**				
Alendronate (ALN) 5mg → 10 mg					ALN 5 mg				
					ALN 10 mg				
					PBO				
Placebo (PBO)									
Actonel									
Years 0-3			**Years 4-5**		**Years 6-7**		**Year 8**	**Years 9-10**	
RIS 5 mg			RIS 5 mg		RIS 5 mg		OFF	RIS 5 mg	
PBO			PBO		RIS 5 mg		OFF	RIS 5 mg	
Boniva									
Oral (Years 0-2)		**(Years 3-5)**							
Ibandronate (IBA) 100mg		IBA 100 mg q mo							
IBA 150 mg qmo		IBA 150 mg q mo							
IV (Years 0-2)		**(Years 3-5)**							
IBA 2 mg IV q2 mo		IBA 2 mg iv q2mo							
IBA 3 mg IV q3 mo		IBA 3 mg iv q3mo							
Reclast									
Years 0-3			**Years 4-6**						
Zoledronic acid (ZOL) 5 mg			ZOL 5 mg						
			PBO						
PBO			ZOL 5 mg						

Bone mineral density and fracture events will be presented separately for each bisphosphonate product.

3.2 Bone Mineral Density (BMD) Results

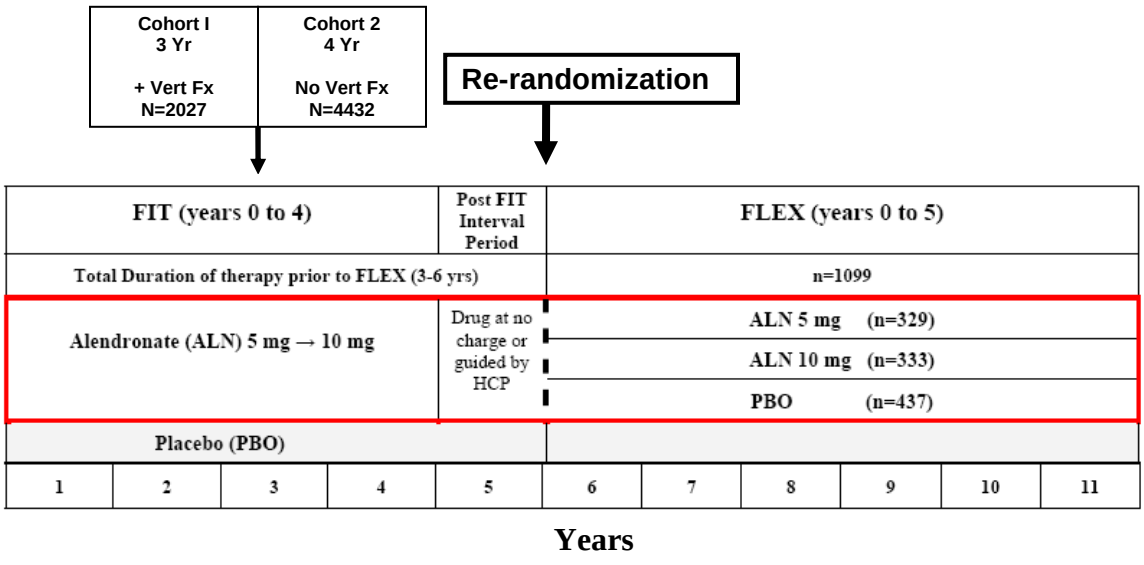
BMD has been used as a secondary endpoint and a surrogate marker for fracture risk in osteoporosis trials. However, preservation or enhancement of bone mass/bone mineral density provides only suggestive evidence that it reduces fractures. Therefore, for drug approval, fracture studies (usually 3 years in duration) must also be conducted to document reduction of fracture incidence.

3.2.1 Fosamax

Figure 2 shows the schematic for the Fosamax Fracture Intervention Trial (FIT) and the FIT Long-Term Extension (FLEX). Subjects enrolled in FIT (n=6,459) had either vertebral fractures at baseline (Cohort 1) or no vertebral fractures at baseline (Cohort 2). The study

included subjects who were 55 to 80 years of age, postmenopausal for at least 2 years, and had femoral neck BMD ≤0.68 g/cm^2 (which would correspond to a T-score of ≤ -1.6 using updated norms). Patients in FIT were initially randomized to alendronate 5 mg or placebo daily for up to 4 years. All subjects in the alendronate 5 mg group were increased to the approved 10 mg dose after 2 years of treatment. The FLEX study then enrolled 1,099 subjects who had previously received alendronate during FIT (from cohorts 1 or 2) and re-randomized them to either continued alendronate (5 mg or 10 mg) or placebo for an additional 5 years. The time period between the end FIT and the beginning of FLEX ranged from 0-2 years. During this time, subjects either received free drug from the sponsor or were directed to continue alendronate by their healthcare provider. The average duration of alendronate use prior to the start of FLEX was 5 years.

Figure 2: Schematic of the FIT/FLEX studies



Prior to showing the results from FLEX, results from the FIT 3 and 4-year studies are reviewed below in **Figure 3**. The graphs show the change in BMD from baseline over time for each cohort. At the femoral neck, those taking alendronate had increases in BMD (about 4%) while those taking placebo had decreases below baseline. At the lumbar spine, there were greater increases in BMD (6-7%) in the alendronate group with some increases in the placebo group (1-2%). The BMD results from both cohorts were similar.

Figure 3: Original Data from FIT 3-year and 4-year BMD

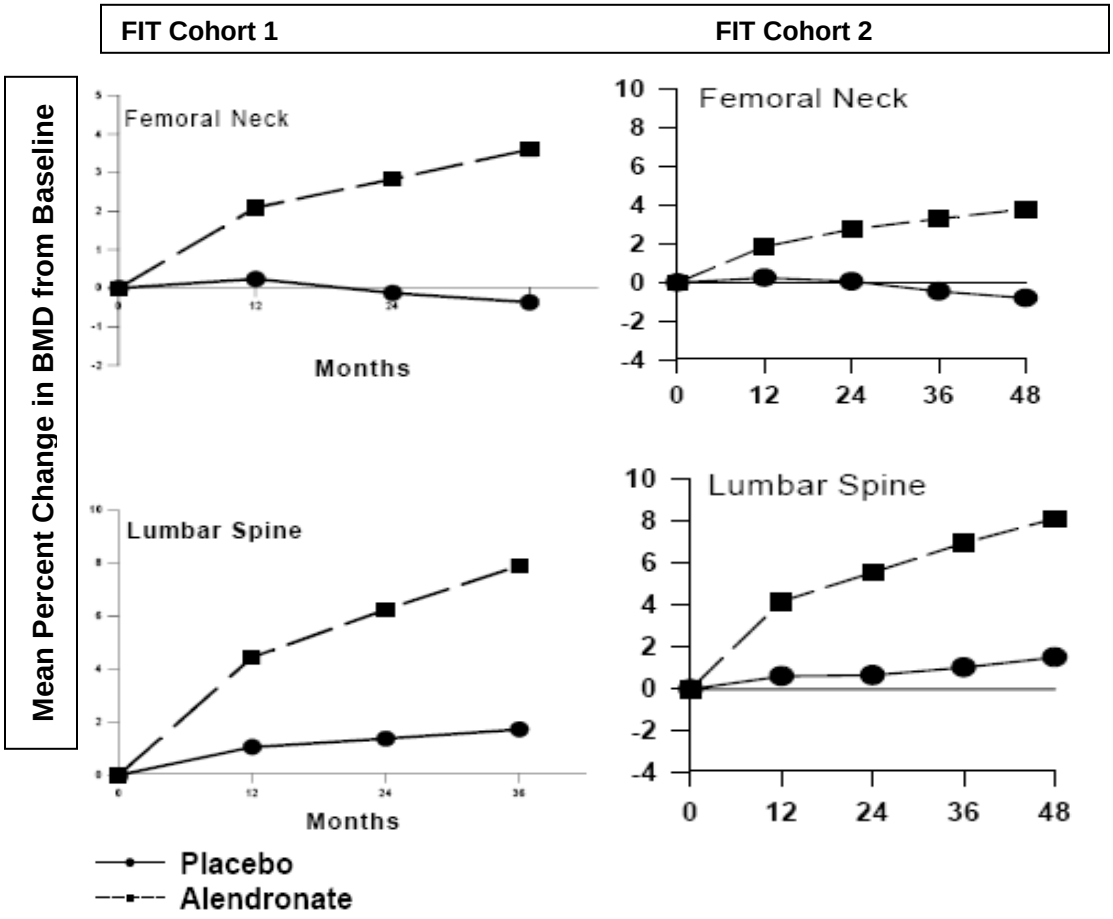
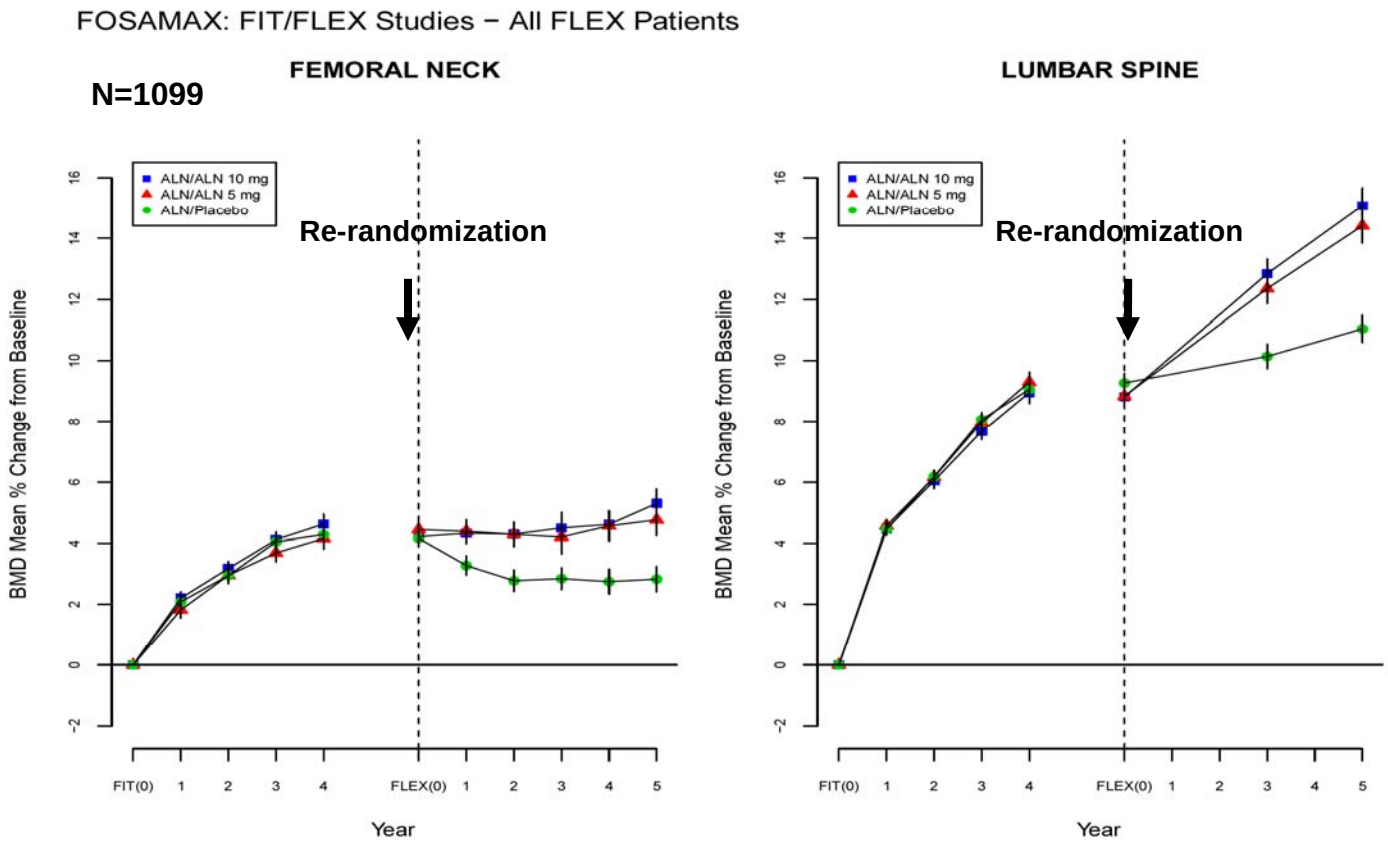


Figure 4 shows the FIT/FLEX data for those 1,099 subjects who entered FLEX. After re-randomization at the start of FLEX, a plateau effect is seen at the femoral neck in those continuing active therapy (either 5 mg or 10 mg), while those re-randomized to placebo had an initial decrease in BMD followed by a plateau that remained above the FIT baseline. BMD at the lumbar spine continued to increase in all groups but to a lesser extent in those switched to placebo.

These results indicate that there is continued BMD efficacy for active therapy but also that the BMD effects persist up to 5 years after alendronate is discontinued.

Figure 4: Fosamax FIT/FLEX BMD Results

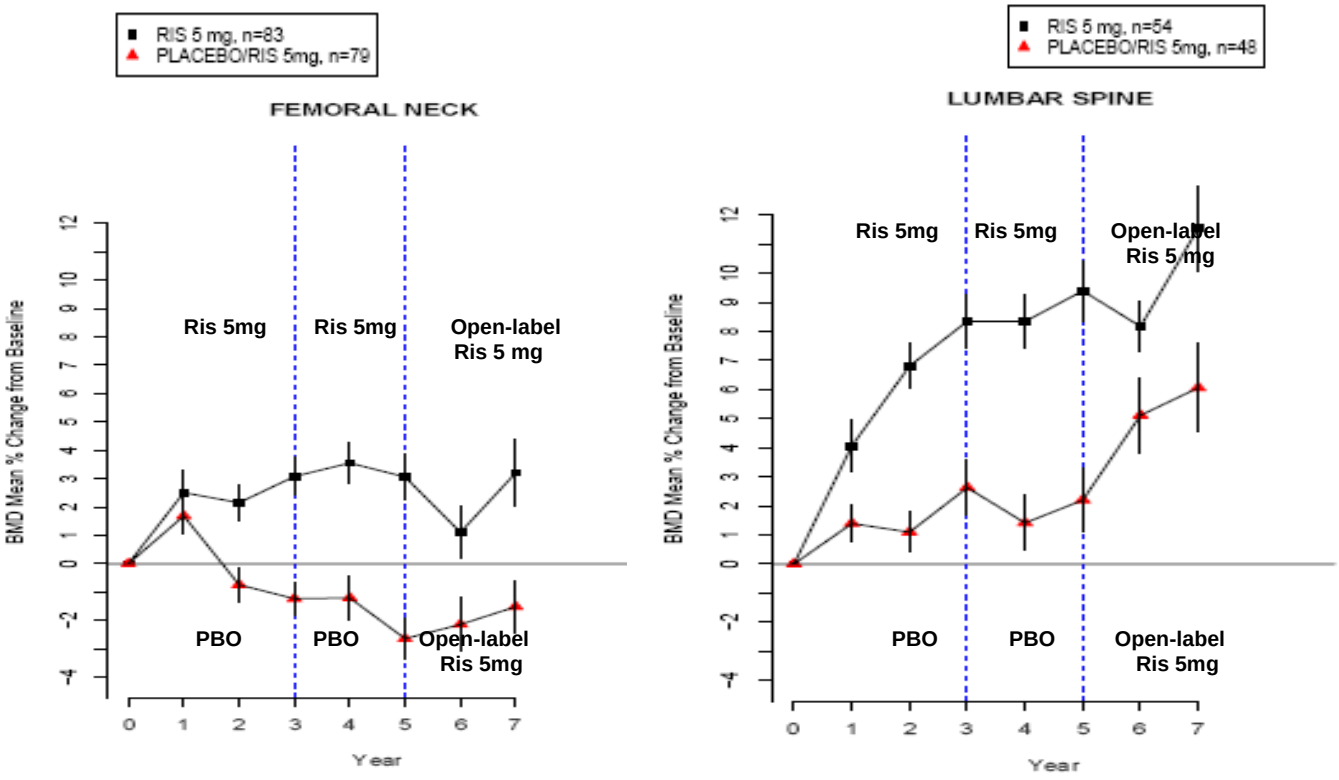


3.2.2 Actonel

The long-term Actonel data included two studies, denoted here as RVE and RVN. Both studies had an initial 3-year study (year 0-3) followed by an additional 2-year time period (year 4-5) where the original treatment groups were extended. The RVE study then had an additional 2-year open-label treatment period (years 6-7) followed by a 1-year drug holiday (year 8), and then 2 additional years of open-label risedronate (years 9-10). The study included women who were at least 5 years postmenopausal and ≤ 85 years age with vertebral fractures at baseline. Combined BMD data through year 7, representing the longest continuous risedronate therapy, are shown in **Figure 5**.

For the continuous risedronate group (shown in black), results are similar to what was seen for Fosamax (FLEX), with overall maintenance of BMD at the femoral neck and increases at the lumbar spine. The placebo arm portion (shown in red) through year 5 is similar to the placebo phase of the FIT 3- and 4-year studies, with BMD falling below baseline at the femoral neck and increasing at the lumbar spine.

Figure 5: Actonel BMD Results

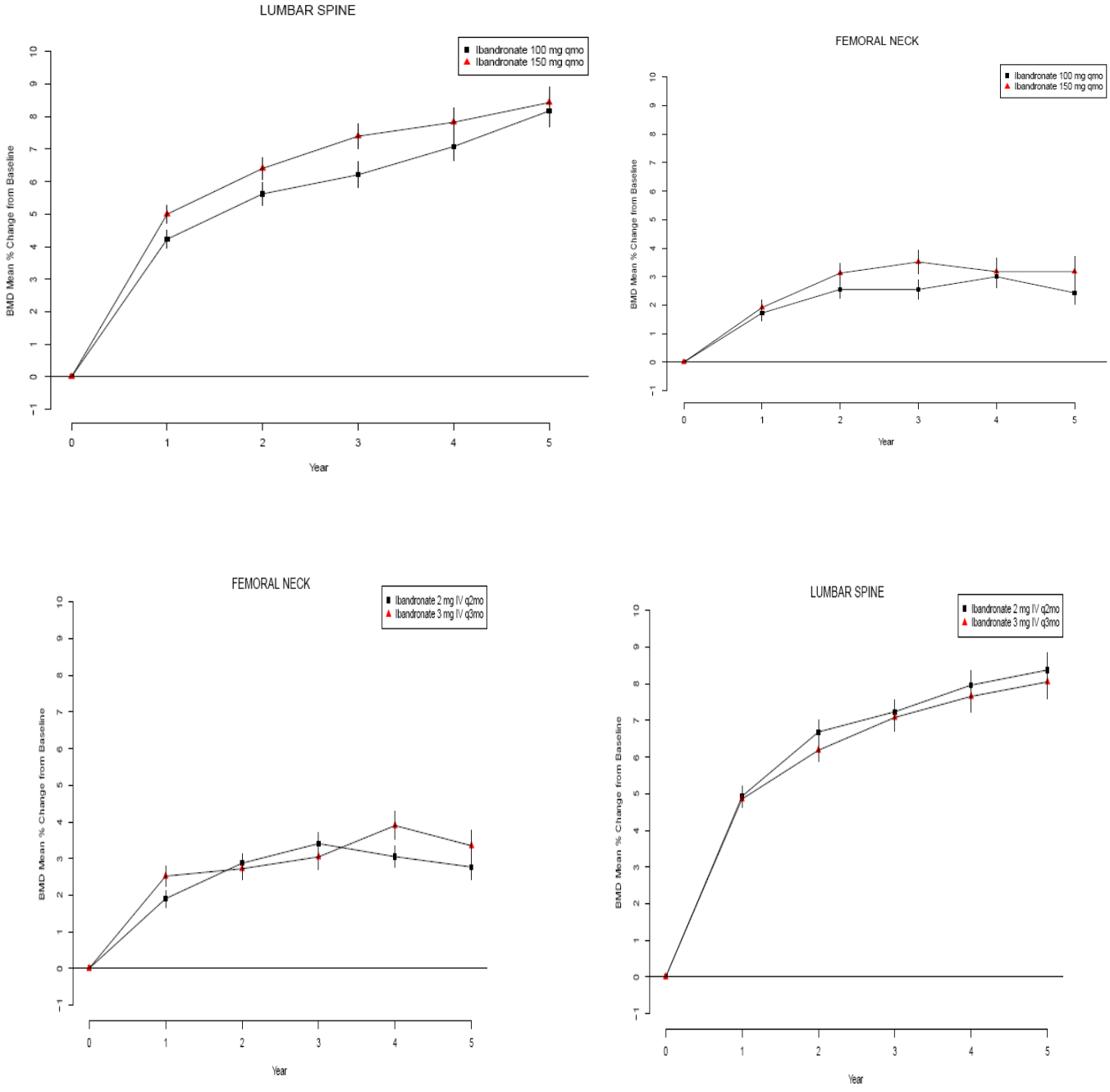


3.2.3 Boniva

The two long-term Boniva studies were 5 years in duration and investigated various doses of oral and intravenous ibandronate. In the oral study, subjects were randomized to receive either 2.5 mg daily, 100 mg monthly (either as a single 100 mg dose or 2 doses of 50 mg each) or 150 mg monthly, for the first two years (years 0-2) of the core study followed by either 100 mg or 150 mg monthly in open-label fashion for the remaining 3-year extension (years 3-5). Patients were allocated to the two open-label ibandronate regimens based on the double-blind regimen received in the core study. The IV study was similar in design with initial doses of 2.5 mg po, 2 mg IV every 2 months, or 3 mg IV every 3 months for 2 years followed by either open-label 2 mg IV every 2 months or 3 mg IV every 3 months for the remaining 3 years based on the original double blind regimen. The long-term extension period did not contain a placebo group nor any other non-ibandronate group.

Figure 6 shows the data for those subjects who entered both the 2-year core and 3-year extension periods. The approved 150 mg daily oral dose and the 3mg q3 months intravenous dose show similar results as the previously shown bisphosphonates. No comment can be made on BMD effect following discontinuation of ibandronate therapy as this study was not designed in that fashion.

Figure 6: Boniva BMD Results (oral)

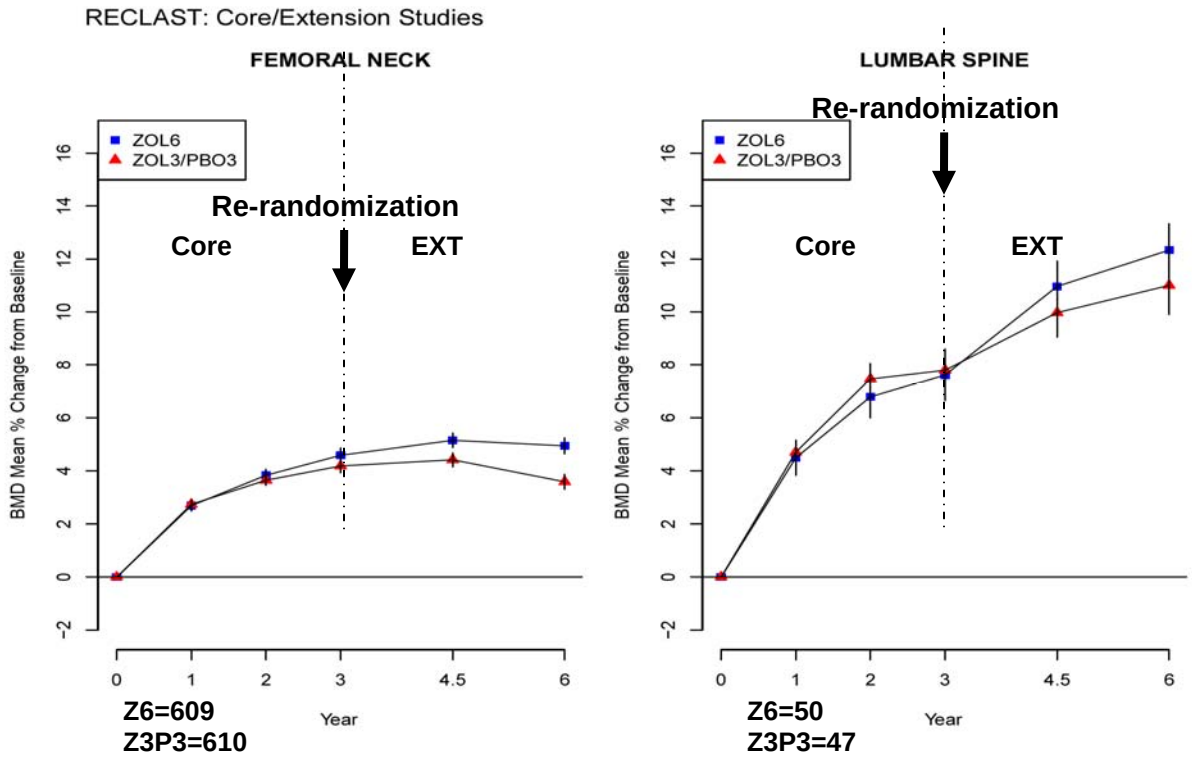


3.2.2 Reclast

Reclast or zoledronic acid data included 6 years of continuous zoledronic acid exposure. The Reclast core study was the 3-year registration trial that enrolled 7736 postmenopausal women with either vertebral fractures at baseline or an osteoporotic range T-score with or without the presence of vertebral fractures. Subjects were randomized to receive zoledronic 5 mg IV yearly or placebo. The 3-year extension study enrolled 1233 subjects who had previously received zoledronic acid 5 mg in the core study and then re-randomized them to continued zoledronic acid 5 mg or placebo.

Figure 7 shows the data for those 1219 subjects who entered both the core and extension periods and had available data. Note that only a small subset of subjects had planned lumbar spine DXAs. These results are similar to the bisphosphonate data previously presented with BMD plateauing at the femoral neck with continued increases at the lumbar spine on active therapy. For those re-randomized to placebo, there were decreases in BMD at the femoral neck (still above baseline) with continued but smaller increases at the lumbar spine.

Figure 7: Reclast BMD Data



3.2.5 BMD Summary

Based on BMD data, several trends were seen following continuous exposure to the class of bisphosphonates for 5 to 10 years. At the femoral neck, there was maintenance of BMD without evidence of increasing BMD benefit with continued treatment. Those who were re-randomized to placebo had modest decreases in BMD with evidence of a plateau effect that

persisted during the off-treatment period. Continued BMD benefit when discontinuing treatment persisted for the remainder of the respective studies and ranged from 3-5 years, however, the true duration of BMD benefit has not been adequately defined. At the lumbar spine, BMD continued to increase in the active therapy groups as well as in the re-randomized placebo groups but to a lesser degree. Some of the BMD effect seen at the lumbar spine in subjects re-randomized to placebo may be attributable to the increase in lumbar spine osteophytes in subjects over 60 years of age that reportedly contribute substantially to lumbar spine BMD measurements.[28]

Overall, it appears that the effect on BMD persists for an undetermined time period but at least 3-5 years once bisphosphonates are discontinued.

3.3 Fracture Results

Fracture studies have previously confirmed the three-year fracture efficacy of the approved drug products for the treatment of osteoporosis. This review focuses on fracture data from the long-term studies under review. Individual fracture data will be presented and will be grouped into multiple-year time periods based on the study-specific fracture collection methods (i.e. when morphometric radiographs were obtained). These numbers may vary from sponsor-presented data as subjects with multiple fractures per period were only recorded once and are presented as the number of subjects with at least one fracture during each period.

Due to the relative small number of fractures in these studies compared to the fracture registration trials, fractures were also pooled across studies. This review focused on the duration of use, therefore, the patients numbers in the pooled analysis include only those subjects who were taking active therapy for the entire study duration and do not include drop-outs or last observation carried forward (LOCF) values.

It should be noted that the discussion and presentation of osteoporotic fractures include both clinical osteoporotic fractures and morphometric vertebral fractures. Non-osteoporotic fractures, including fractures of the fingers, toes, skull and face were excluded.

3.3.1 Fosamax

Table 9 shows an FDA analysis of the fracture data for those subjects who were enrolled in both FIT and FLEX. All subjects received alendronate (5mg and then 10 mg) during FIT and then were re-randomized to continued alendronate 5 mg or 10 mg or received placebo. The values represent the percent of patients with at least 1 osteoporotic fracture during each treatment period. The patient numbers in the denominators represent only those subjects who enrolled in FLEX and account for 15% of all subjects who completed the 3- and 4-year FIT studies.

[28] Greenspan, S., Maitland, L., Myers, E., Krasnow, M., & Kido, T. (1994). Femoral Bone Loss Progresses with Age: A Longitudinal Study in Women Over Age 65. JBMR, 9(42):1959-1965.

Table 9: Osteoporotic Fractures - Fosamax
Percent of Patients[a] with at least 1 osteoporotic fracture
% (n patients with fx/N total patients)

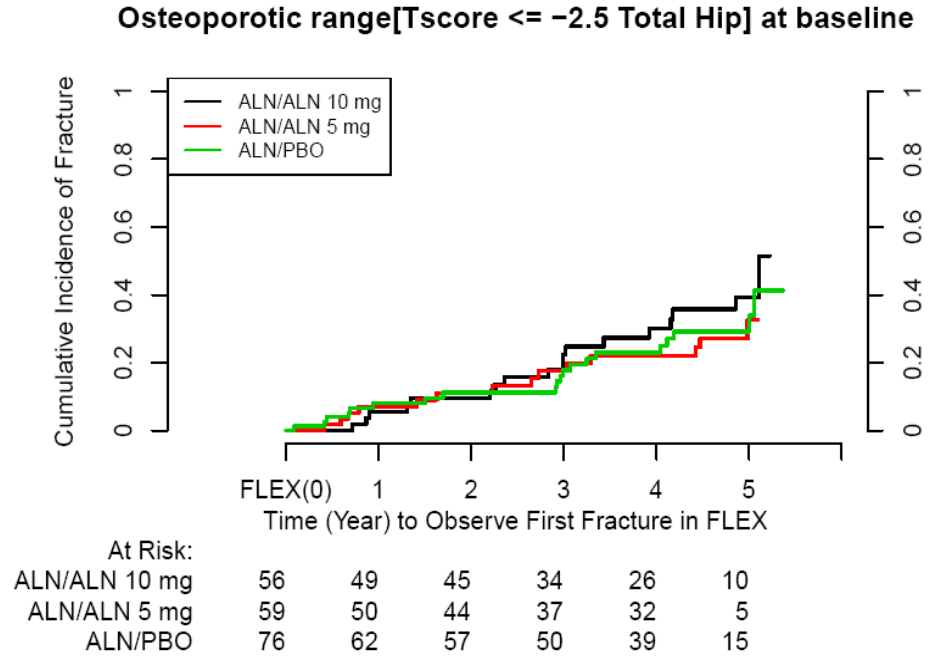
FIT Treatment/FLEX Treatment	FIT (Years 0-4)	FLEX (Years 0-5)
ALN* / ALN 10 mg	12.6% (42/333)	18.6% (62/333)
ALN / ALN 5 mg	9.7% (32/329)	16.7% (55/329)
ALN / Placebo	9.8% (43/437)	16.9% (74/437)
All ALN / Any Treatment	10.6% (117/1099)	
Background Placebo	21%	
ALN/ALN 5 + ALN/ALN 10 mg (combined)		17.7% (117/662)

[a]Patients who were enrolled in both FIT and FLEX
*ALN = alendronate

The percent of patients with at least one osteoporotic fracture during FIT ranged from 9.7-12.6%. But when all the FIT subjects from the FIT/FLEX population are pooled, the fracture rate is 10.6% (117/1099), which is still considerably lower than the overall FIT background placebo fracture rate of 21%. During FLEX, there was an increase in the fracture rates compared to FIT, possibly attributable to a combination of factors, including a higher fracture risk subject group choosing to enroll in FLEX, and an older patient population that is at higher risk of fracture based on advancing age. When the active treatment groups in FLEX are compared either individually (16.7% and 18.6%) or collectively (17.7%, 117/662) with the alendronate/placebo (ALN/Placebo) rate of 16.9%, it appears that those who switched to placebo had similar fracture rates to those continuing active therapy. These results would question, from a fracture-efficacy perspective, whether there is an advantage to continued therapy beyond four years.

To investigate fracture rates when continuing therapy with alendronate compared to stopping therapy, an FDA exploratory analysis of the FLEX fracture data was performed. Various baseline characteristics were evaluated to see if there were any subgroups that showed time-to-fracture differences between treatment groups. Using all FLEX subjects, no differences across treatment groups were noted. However, when subjects were also grouped by their T-score at FLEX baseline, see **Figure 8**, a worsening trend was seen in the cumulative incidence of fractures over time in those who had a T-score at the total hip in the osteoporotic range (≤ -2.5). It is likely that these subjects who continued to have osteoporotic BMD at FLEX baseline would be at a high risk of fracture. In the first 3 years of FLEX, the cumulative incidence of fractures was very similar across all treatment groups. However, by year 3 of FLEX, corresponding to 8 years of continuous alendronate exposure, the curves tend to separate across the three treatment groups in favor of those re-randomized to placebo or alendronate 5 mg. The sample size is quite small in the later years of FLEX, so interpretation of this finding is difficult.

Figure 8: FLEX Fracture Data by T-score <= -2.5



Note: The stepwise nature of the curves reflects the manner of morphometric data collection.

In a published post hoc analysis[29] of the FLEX trial, the investigators showed that fracture benefit was limited to the clinical vertebral fracture group (relative risk reduction = 63%). No benefit was seen for morphometric fractures or for all vertebral fractures combined (morphometric and clinical vertebral). In a separate analysis[30], fracture benefit was seen for non-vertebral fractures in FLEX but only in a very specific patient population, those without vertebral fractures at baseline and who also had a T score < -2.5.

3.3.2 Actonel

Fracture results following long-term and continuous risedronate exposure are shown in **Table 10**. Comparing the two treatment groups, the percentage of patients with at least one fracture was lower in the continuous risedronate exposure treatment group compared to the placebo group across all three time periods, with the gap narrowing in years 6 to 7 attributable to those placebo subjects starting risedronate at year 6. Also, within the continuous risedronate exposure group, the fracture rates decreased over time (20.5% vs 13.2%) suggesting continued fracture benefit with continued therapy but the number of total subjects is relatively small.

[29] Black, D., Schwartz, A., Ensrud, K., Cauley, J., Levis, S., Quandt, S., et. al. (2006). Effects of Continuing or Stopping Alendronate After 5 years of Treatment: The Fracture Intervention Trial Long-term Extension (FLEX): A randomized Trial. *JAMA*, 296(24):2927-2938.

[30] Schwartz, A, Bauer, D., Cummings, S., Cauley, J., Ensrud, L., Palermo, L., et al. Efficacy of Continued Alendronate for Fractures in Women with and without Prevalent Vertebral Fracture: The FLEX Trial. *JBMR*, 25(5):976-982.

Table 10: Osteoporotic Fractures - Actonel
Percent of patients with at least 1 osteoporotic fracture
% (n patients with fractures/ N total patients)

Treatment Year 0-3/Year 4-5/Year 6-7	Year 0 - 3	Year 4 - 5	Year 6 - 7
Ris* 5 mg/Ris 5mg/Ris 5 mg	20.5% (17/83)	19.3% (16/83)	13.2% (11/83)
Placebo/Placebo/Ris 5mg	32.1% (26/81)	32.1% (26/81)	16.0% (13/81)

*Ris=risedronate

3.3.3 Boniva

Only clinical vertebral and non-vertebral fractures were recorded in the two 5-year studies. Morphometric vertebral fracture assessments were not included in these studies. Therefore, fracture capture was incomplete. These data were not included in the additional fracture analyses.

3.3.4 Reclast

Fracture results from the Reclast long-term study are shown in **Table 11**. No difference in the percent of patients with at least 1 osteoporotic fracture was seen during the first three years. For years 4 to 6, a numerical decrease in the number of subjects with fractures was seen in those continuing Reclast therapy. When the difference was tested between groups, the difference was borderline significant (difference of 0.034, p-value 0.0502) and did not account for multiplicity. Therefore, no robust fracture benefit was seen in those continuing therapy.

Table 11: Osteoporotic Fractures - Reclast
Percent of patients with at least 1 osteoporotic fracture
% (n patients with fracture / N total patients)

Treatment	CORE Years 0-3	EXTENSION Years 4-6
Reclast/Reclast (Z6)	10.1% (62/616)	8.6% (53/616)
Reclast/Placebo (Z3P3)	9.6% (59/617)	12.0% (74/617)
Background Placebo	**20%**	
		Difference 0.034 (p=0.0502)

In an effort to assess if the subgroups noted to show benefit in the Fosamax trials, similar analyses were performed for the Reclast data. Continued therapy with Reclast showed a fracture benefit in morphometric vertebral fractures compared to those subjects re-randomized to placebo (relative risk reduction of 52%). But no difference was seen for clinical vertebral fractures. These results differ from the Fosamax findings where fracture benefit in clinical fractures was seen.

3.3.5 Pooled Fracture Data

In an effort to look for fracture trends in patients with prolonged and continuous bisphosphonate exposure, all available fracture data were pooled for Fosamax, Actonel and

Reclast incorporating 1200 patients. These 1200 patients represent those subjects who continued active therapy for the entire study duration. Those patients who discontinued active therapy (i.e., dropped out of the study) were excluded from this analysis. Those re-randomized to placebo were also excluded from the analysis but these rates are shown for reference.

Table 12: Pooled Fractures
Percent of patients with at least 1 fracture per time period
% (n patients with fracture / N total patients)

	Year 0-3	Year 4-5	Year 6-9	Year >9
At Least 1 Fracture Continuous Active Therapy (ALN + ZOL + RIS)*	**9.7% (116/1200)**	**6.0% (72/1200)**	**10.6% (62/585)**	**9.3% (48/517)**
At Least 1 Fracture 3 Years Active then Placebo# (ALN/Placebo + ZOL/Placebo)	**8.2% (79/968) On active drug**	**8.6% (83/968)**	**8.8% (31/351)**	**8.0% (28/351)**
Background Placebo	**20.4%**			

* ALN=alendronate, ZOL= zoledronic acid, RIS=risedronate
# Includes only patients from alendronate and zoledronic acid trials because there was no risedronate/placebo group studied

Comparing rates for those with at least one fracture over time who were maintained on active therapy (**Table 12**), there appears to similar fracture rates over time, with the exception of treated subjects in Years 4-5. The reason for improvement in the fracture rate in this time period is not clear. The fracture rates for those exposed for greater than 9 years are similar to those seen in the original 3-year fracture period, which suggests that there is not a deterioration in fracture efficacy. The fracture rates for those previously on active therapy who switched to placebo remained constant over time (8-9%). Rates for both groups remain below the background placebo rate of 20.4%. It should be noted that beyond year 6, the cohort size decreases markedly because of the different designs and durations of the trials included in the analysis. Overall, these data raise the question of whether there is continued fracture benefit achieved with long-term bisphosphonate therapy when compared with discontinuation of bisphosphonates after three to four years of therapy.

When looking at differences between groups based on baseline demographics across the various bisphosphonate exposure windows using baseline demographics, not surprisingly, patients who were over 70 years of age, had a fracture history at baseline, or had a femoral neck T score ≤-2.5, well recognized risk factors for fracture, were more likely to have sustained a fracture despite continued bisphosphonate exposure (**Table 13)**.

Table 13: Characteristics of patients with continued bisphosphonate exposure who had at least 1 fracture by exposure time period

Baseline Characteristic	Patients with at least 1 osteoporotic fracture			
	Year 0-3	Year 4-5	Year 6-9	After Year 9
Age group (years)				
≤ 60	11.4% (9/79)	6.6% (5/76)	5.1% (4/79)	5.6% (4/72)
61-70	7.7% (44/569)	5.4% (21/386)	9.1% (29/318)	8.0% (24/299)
> 70	11.4% (63/552)	8.3% (46/552)	15.4% (29/188)	13.7% (20/146)
Baseline Fracture				
Yes	10.3% (71/686)	7.0% (48/686)	13.8% (47/340)	10.83% (30/277)
No	8.4% (43/509)	4.8% (24/509)	5.8% (14/242)	7.50% (18/240)
Femoral Neck T-score				
<=-2.5	11.4% (72/632	8.5% (54/632)	15.3% (28/183)	9.49% (13/137)
-2.5 to -1.0	8.1% (44/545)	2.9% (16/545)	8.6% (34/395)	9.23% (35/379)
>-1.0	0% (0/8)	12.5% (1/8)	0% (0/6)	0% (0/1)
Total	9.67% (116/1200)	6.0% (72/1200)	10.60% (62/585)	9.28% (48/517)

3.3.6 Fracture Summary

The fracture data suggest that with continued drug exposure, there is no clear benefit nor harm for overall osteoporotic fracture risk. It appears that patients with well-recognized risks for fracture (baseline history of fracture, age older than 70 years, and those remaining in the osteoporotic T-score range) are more likely to fracture despite continued bisphosphonate therapy. There was no clear and consistent benefit across the trials for any particular fracture type.

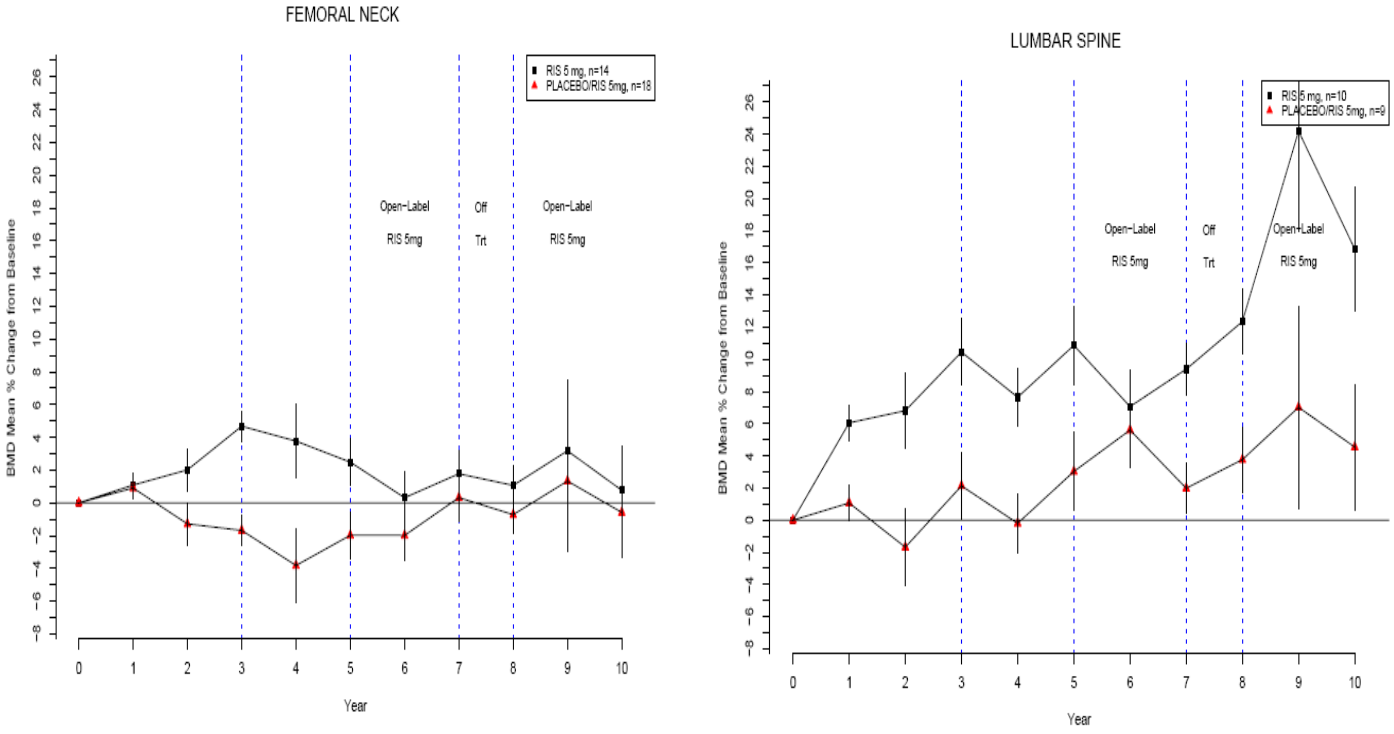
For those who have been previously treated with bisphosphonates who then discontinued therapy, there appears to be no difference in fracture rates compared to those who continued active therapy. In fact, the fracture incidence in this group remained stable in the pooled analysis. Three to five years of previous drug exposure may confer this benefit. These results suggest no significant advantage of continuing drug therapy beyond 5 years.

3.4 Drug Holiday

3.4.1 BMD Results

The only available data on a drug holiday is from year 8 of the Actonel study where all subjects were discontinued for 1 year followed by resumption of risedronate therapy for 2 years (years 9/10). **Figure 9** shows the BMD results for the 32 subjects enrolled in years 8-10. Prior to year 8, patients received either continuous risedronate (shown in black) or placebo for five years followed by open-label risedronate (shown in red). BMD results were similar to what was previously presented showing maintenance of BMD at the femoral neck and increases at the lumbar spine. Interpretation of the data is quite difficult given the small sample size.

Figure 9: Actonel – Drug Holiday BMD Data



3.4.2 Fracture Results

Table 14 presents fracture results for those 32 subjects continuing into years 9/10. There was only 1 new subject with fracture occurring in year 8 in the risedronate group and 5 subjects with fractures in years 9/10 split between the two groups (two occurring in the risedronate group, and 3 occurring in the group switched to placebo). With such small numbers the data are limited and an adequate analysis was not possible. Note: Subjects in the placebo/risedronate group, previously received placebo for the first 5 years.

Table 14: Drug Holiday – Actonel 10-year Fracture Results
Percent of subjects with at least one fracture during each time period
% (n patients with fractures / N total patients)

	Year 1-3	Year 4-5	Year 6-7	Year 8	Year 9-10
Risedronate 5 mg	RIS 5mg	RIS 5mg	RIS 5mg	OFF	RIS 5mg
	28.6% (4/14)	21.4% (3/14)	0% (0/14)	7.1% (1/14)	14.3% (2/14)
Placebo/Ris 5mg	PBO	PBO	RIS 5mg	OFF	RIS 5mg
	22.2% (4/18)	27.8% (5/18)	22.2% (4/18)	0% (0/18)	16.7% (3/18)

3.4.3 Monitoring During Drug Holiday

With a discussion regarding implementing a drug holiday come further questions that need to be answered. These include:

- Should all or a subset of patients be recommended for a drug holiday?

- What factors should be used to determine if a drug holiday is indicated?
- If a drug holiday is implemented, what factors should be used to predict *who* should resume bisphosphonate therapy?
- If a drug holiday is implemented, what factors should be used to predict *when* therapy should be resumed?

Scant data on bisphosphonate drug holiday are available. Many scientific opinions have been published suggesting cessation of therapy but are based on review of studies that did not include a drug holiday phase.

Two studies have provided some data on predictive factors at the time of bisphosphonate drug discontinuation and subsequent BMD monitoring. A post-hoc analysis of the FLEX trial[31] showed that femoral neck BMD after the initial 5 years of alendronate treatment predicted future alendronate efficacy for the prevention of non-vertebral fractures but only in patients without baseline vertebral fractures and who also had a T-score $\leq$ -2.5. Based on no differences in fracture risk in patients who did or did not lose bone during the initial 5-year period, the authors also suggest that BMD changes and, therefore BMD monitoring, is not useful in predicting who will most likely benefit from continued alendronate therapy.

A follow-up abstract[32] also using the FLEX database was presented at the 2010 ASBMR Annual Meeting, and investigated whether serial BMDs at yearly intervals could predict fracture risk. The authors concluded that hip BMD at the time of alendronate discontinuation strongly predicted the risk of clinical fractures over the next five years. In addition, as suggested in the earlier publication, following BMD changes over 1- and 2-years intervals after alendronate discontinuation were not useful.

Based on these reports, BMD at the time of bisphosphonate discontinuation may be important in a drug holiday management decision. But there are no studies that define an appropriate drug holiday duration as well as the use of surrogate markers of increased risk, particularly since BMD change is not likely useful.

3.5 Bone Quality

Long-term bone histomorphometry data are available from 18 subjects who completed FIT and FLEX trials and are shown in the right hand columns of **Table 15** below. Nine subjects were re-randomized to placebo, while the remaining nine continued active therapy with alendronate. There were no statistical differences in bone integrity/microstruture, mineralization or bone turnover parameters between groups. Data from the two Primary Phase III Postmenopausal 3-year studies (the alendronate registration trials) are included as reference in the middle columns. Of the 418 subjects enrolled in the Primary Phase III studies

[31] Schwartz, A, Bauer, D., Cummings, S., Cauley, J., Ensrud, L., Palermo, L., et al. Efficacy of Continued Alendronate for Fractures in Women with and without Prevalent Vertebral Fracture: The FLEX Trial. *JBMR*, 25(5):976-982.

[32] Bauer, D,, Schwartz, A., Palermo, L., Cauley, J., Ensrud, K., Hochberg, M, et al. Utility of Serial BMD for Fracture Prediction After Discontinuation of Prolonged Alendronate Therapy: The FLEX Trial, Abstract presented to ASBMR Annual Meeting, Toronto 2010

(270 receiving alendronate [5, 10 or 20/5mg] and 148 receiving placebo), biopsies were performed in 20 subjects receiving alendronate 10 mg and 50 subjects receiving placebo.

Table 15: Bone Histomorphometry Data

Primary Phase III (3-year exposure) vs FLEX (10-year exposure)

			Primary Phase III Studies			FLEX		
Parameter	**Normal Range****	**Statistic**	**ALN 10mg**	**PBO**	**Difference ALN vs PBO**	**ALN/ALN**	**ALN/PBO**	**Difference ALN vs PBO 95% CI**
Trabecular Number (#/mm)	1.2 – 2.00	N **Mean**	NR	NR	NR	9 **1.31**	9 **1.29**	0.02 (-0.22, 0.26)
Trabecular Thickness (µm)	93 - 185	N **Mean**	NR	NR	NR	9 **148**	9 **142**	6.33 (-25.08, 37.75)
Bone Volume (BV/TV)	14.0 – 30.0	N **Mean**	NR	NR	NR	9 **19.50**	9 **18.33**	1.17 (-4.55, 6.89)
Osteoid surface (OS/BS)(%)	7.0 – 25.0	N **Mean**	NR	NR	NR	9 **9.95**	9 **11.63**	-1.68 (-7.25, 3.90)
Osteoid volume (OV/BV)(%)	0.30 – 3.10	N **Mean**	19 **0.12***	41 **1.12***	NR	9 **0.94**	9 **1.06**	-0.12 (-0.69, 0.45)
Osteoid thickness (O.Th)(µm)	5.5 – 12.0	N **Mean**	18 **7.32**	41 **10.71**	NR	9 **5.07**	9 **4.76**	0.31 (-0.29, 0.91)
Mineral Apposition Rate (µm/d)	0.360 – 0.630	N **Mean**	12 **0.63**	40 **0.59**	NR	9 **0.52**	9 **0.56**	-0.03 (-0.17, 0.11)
Mineralizing Surface % (MS/BS)	1.0 –13.5	N **Mean**	19 **0.25***	41 **6.37***	NR	9 **1.43**	9 **3.03**	-1.60 (-4.27, 1.08)

* Median reported due to skewed distribution
** Healthy postmenopausal Caucasian women (n=34)[33]

On qualitative assessment, there was no evidence of woven bone, marrow fibrosis, abnormal osteoid, marrow dyscrasia or osteomalacia.

Individual bone histomorphometry data are shown in **Table 16**. While there were outliers seen, there were no major trends by treatment group.

[33] Recker, R., Kimmel, D., Parfitt, M., Davies, M., Keshawarz, N., & Hinders, S. (1988). Static and Tetracycline-Based Bone Histomorphometric Data from 34 Normal Postmenopausal Females. *JBMR*, 3(2):133-144.

Table 16: Individual Bone Histomorphometry Data - FLEX

Pt No	Tx Group	Evaluable?	Dbl Lbl ?	TB.N (#/mm)	Tb.Th (µm)	Bone Vol BV/TV (%)	Osteoid Surface OS/BS (%)	Osteoid Vol OV/BV (%)	Osteoid Thick OsTh (µm)	MAR (µm/d)	Mineral Surface MS/BS (%)
8308	ALN/PBO	Y	Y	1.26	126	15.87	7.35	0.7	4.8	0.73↑	0.28↓
8317	ALN/PBO	Y	Y	1.06↓	153	16.32	20.03↑	1.88↑	5	0.49	10.75↑
8324	ALN/PBO	Y	Y	0.99↓	123↓	12.17↓	12.92	1.39	5	0.45	0.71
8325	ALN/PBO	Y	Y	1.19	131	15.58	8.11	0.77	4.5	0.56	1.16
8357	ALN/PBO	Y	Y	1.45	107↓	15.51	6.19	0.67	4.8	0.44	1.71
8398	ALN/PBO	Y	Y	1.73↑	174	30.08↑	10.43	0.84	5.3	0.5	1.86
8399	ALN/PBO	Y	Y	1.47↑	121	17.8	14.73	1.21	3.8↓	0.64	4.38↑
8410	ALN/PBO	Y	Y	1.04↓	189↑	19.71	8.44	0.63	5	0.77↑	0.63
8416	ALN/PBO	Y	Y	1.44	153	21.96	16.48	1.43	4.6	0.42	5.79↑
8307	5 mg	Y	Y	1.14	103↓	11.74↓	9.53	1.31	5.3	0.61	0.84
8338	5 mg	Y	Y	1.53	137	20.99	13.17	0.96	4.2	0.24↓	0.38↓
8372	5 mg	Y	Y	1.57↑	193↑	30.22↑	21.26↑	2.04↑	6.6↑	0.58	5.41↑
8409	5 mg	Y	Y	0.95↓	149	14.13	10.04	0.81	5	0.78↑	0.81
8451	5 mg	Y	Y	1.36	201↑	27.37	3.99↓	0.29↓	4.8	0.55	0.77
8344	10 mg	Y	Y	1.41	156	22.06	4.07↓	0.36↓	5.2	0.45	2.04
8380	10 mg	Y	Y	1.01	169	17.03	8.01	0.46	4.1	0.43	1.24
8384	10 mg	Y	Y	1.52	113	17.1	2.39↓	0.3↓	5.2	0.49	0.19↓
8394	10 mg	Y	Y	1.31	113	14.88	17.13	1.9↑	5.2	0.57	1.21
Source: QBBHQA (double label and evaluable status), QBBHQR (values)											

Therefore, no alterations in bone quality were noted except for a non-statistical decrease in osteoid surface/volume and bone turnover as would be expected from bisphosphonate therapy.

3.5.1 Discussion

BMD data on bisphosphonate exposure out to 10 years appear to demonstrate continued increases in BMD at the lumbar spine and maintenance of BMD at the femoral neck. In patients who discontinue bisphosphonate exposure after 3-5 years, small increases in BMD at the lumbar spine and small decreases in BMD are seen followed by a plateau at the femoral neck for the remainder of the selected studies (range 3-5 years). The total duration of effect is unknown.

Limited fracture data on bisphosphonate exposure out to 10 years appear to demonstrate sustained but no further increase in fracture benefit after 3-4 years of therapy but also no clear evidence of harm or increase in overall osteoporotic fractures. There is also no clear subset of patients which demonstrates continued benefit across studies. In patients who discontinue bisphosphonate exposure after 3-5 years of treatment, fracture incidence rates were relatively constant over time.

In light of all of the risk-benefit challenges with the bisphosphonate class, these data suggest that bisphosphonate therapy could be safely discontinued from an efficacy standpoint. However, additional long-term data would be needed to further define an appropriate duration of drug cessation and to determine if interim monitoring is appropriate on an individual basis.

4 Summary

Osteoporosis is a systemic skeletal disease that affects a large number of the U.S. population. There is significant morbidity and mortality associated with osteoporotic fractures, particularly hip fractures. The bisphosphonate medications are highly effective at decreasing the fracture risk associated with osteoporosis, as demonstrated by the required fracture registration trials where morphometric vertebral fracture is the primary endpoint. In addition, recent studies have analyzed the epidemiology of hip fractures from 1996-2006.[34] Using the National Hospital Discharge Survey from 1996 to 2006, the annual hip fracture incidence in patients over the age of 50 years fell from 600/100,000 in 1996 to 400/100,000 in 2006. This occurred at a time when the age of the population is increasing and it has been well documented that age is a major risk facture for osteoporotic fracture. Therefore, despite the increasing age of the population, hospital discharge rates for hip fracture have decreased. Treatment with bisphosphonates and the resultant reduced fracture risk could play a significant role in this finding.

The first bisphosphonate was approved for the treatment and/or prevention of osteoporosis 16 years ago. Over that time period, newly recognized adverse events potentially related to bisphosphonate exposure have occurred and have been labeled accordingly. More recently, very rare adverse events that can have substantial morbidity, namely osteonecrosis of the jaw, atypical subtrochanteric and femoral diaphyseal fractures, and esophageal cancer have raised questions regarding an association with long-term use of bisphosphonates. As part of our ongoing assessment of bisphosphonates, the FDA focused on both the question of the long-term safety and the question of the long-term efficacy of chronic bisphosphonate therapy.

With regard to long-term safety, we have presented our review of all data that are available. Osteonecrosis of the jaw is a very rare event that occurs predominantly in cancer populations with use of the intravenous bisphosphonate preparations. In the osteoporosis population, ONJ has been reported with oral bisphosphonate use. Data from an FDA-sponsored study suggest an increased prevalence of ONJ with increased duration of exposure to oral bisphosphonates, with the highest prevalence occurring at 4 or more years of use. However, we are cautious regarding this interpretation because the study was not designed to determine causation. Confirmatory longitudinal studies with appropriate comparator groups designed to account for other potential confounding factors are needed. Atypical subtrochanteric and femoral diaphyseal fractures are also very rare events. The incidence of these fractures pale in comparison to typical hip fractures, and may not be specific to bisphosphonate users. The data to date suggest a strong association with bisphosphonate use, although causality has not been determined. There is no agreement regarding cumulative bisphosphonate exposure and a potential association with higher risks of atypical fractures. For esophageal cancer, while there is biologic plausibility, evidence to date remains inconclusive regarding a possible association between oral bisphosphonates and esophageal cancer.

[34] Nieves JW, et.al. Fragility fractures of the hip and femur: incidence and patient characteristics. Osteoporos Int 2010. 21:399-408.

With regard to long-term efficacy, there are clinical trial data available to assess bisphosphonate effectiveness out to ten years. In some cases, the clinical trial features a randomized withdrawal phase. While the data are not as substantial as that seen for the clinical efficacy registration trials, they do allow for some assessment of the long-term efficacy of the bisphosphonate products.

BMD data appear to demonstrate continued increases in BMD at the lumbar spine and maintenance of BMD at the femoral neck out to 10 years of bisphosphonate exposure. In patients who discontinue bisphosphonate exposure after 3-5 years, small increases in BMD at the lumbar spine and small decreases in BMD are seen followed by a plateau at the femoral neck for the remainder of the selected studies (range 3-5 years). There is no evidence of a return to baseline BMD values for the duration of the studies reviewed.

Limited fracture data on bisphosphonate exposure out to 10 years appear to demonstrate that there is sustained but no further increase in fracture benefit after 3-4 years of therapy but also no clear evidence of harm or increase in overall osteoporotic fractures. While different subsets of patients appear to have evidence of benefit with continued therapy, these findings are dependent on the study reviewed. There is no clear subset of patients that has clear benefit with continued therapy confirmed across multiple studies. In patients who discontinue bisphosphonate exposure after 3-5 years of treatment, fracture incidence rates were relatively constant over time.

There are no substantial data available to inform decisions regarding the initiation or duration of a drug holiday.

Review of bone histomorphometry data from the FLEX trial reveals no concerning bone quality findings.

In light of the potential risks that may be associated with long-term use of bisphosphonates for the treatment and/or prevention of osteoporosis, the sum of available long-term efficacy data appears to suggest that bisphosphonate therapy could be safely discontinued for some period of time. However, additional data are needed to further define an appropriate duration of drug holiday and to determine whether interim monitoring could be informative.

Appendix 1: Chang 2003 FDA Review

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D030552

DATE: November 21, 2003

FROM: Jennie T. Chang, Pharm.D., Safety Evaluator

THROUGH: Mark Avigan, M.D., Acting Director
Division of Drug Risk Evaluation, HFD-430

TO: Richard Pazdur, M.D., Director
Division of Oncologic Drug Products (DODP), HFD 150

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510

SUBJECT: Reaction: Osteonecrosis
Drugs: Pamidronate (Aredia) and Zoledronic Acid (Zometa)

EXECUTIVE SUMMARY

This memorandum concerns a consult request of Nancy Scher, M.D., Medical Reviewer, DODP, regarding zoledronic acid-associated osteonecrosis. Interest in this adverse event was stimulated from a cluster of reports submitted recently to FDA's postmarketing database. Additionally, Novartis Pharmaceuticals, the Sponsor for zoledronic acid, recently submitted a "Special Supplement-Changes Being Effected" to include a *Post-Marketing Experience* subsection of the *Adverse Reactions* section of Zometa's package insert to provide information on osteonecrosis. For completeness, pamidronate is also reviewed as it is given intravenously and is from the same therapeutic class, namely biphosphonate-mediated bone resorption inhibitors.

Using the FDA's Adverse Event Reporting System database, a search was undertaken to determine the number of osteonecrosis cases associated with zoledronic acid and pamidronate using the MedDRA High Level Term (HLT) Bone Disorders. Cases were included per physician diagnosis of osteonecrosis. The data lock-points are from the date of marketing for the two bisphosphonates, October 31, 1991 for pamidronate and August 20, 2001 for zoledronic acid, until October 6, 2003.

A total of 53 cases, 30 with pamidronate use, 6 with zoledronic acid use, and 17 with both zoledronic acid and pamidronate use, were found in AERS. All cases, except for two, were domestic. No patients experienced serious sequelae resulting in hospitalization or death.

Because both medications are from the same therapeutic class and it was difficult to determine primary suspect drug, the cases are analyzed together according to medication receipt (see Table 1).

In cases in which the patient received both bisphosphonates, all patients first received pamidronate prior to switching over to zoledronic acid.

Though only cases with use of intravenous bisphosphonates were evaluated here, we also intend to reviewing cases involving oral bisphosphonates and osteonecrosis to determine whether this is a drug class effect.

Our postmarketing data indicate a safety concern exists for zoledronic acid and pamidronate, in reference to osteonecrosis, despite the confounders in these cases. The zoledronic acid and pamidronate labeling should be amended to note that there have been postmarketing cases of osteonecrosis associated with these medications. Additionally, the labeling should state that the recovery time is not immediate, even after discontinuing the bisphosphonates as the half-lives are long. Prescribers should alert patients to report any jaw pain and referral to a dentist or oral surgeon for appropriate treatment is necessary, once bone metastases is ruled out.

BACKGROUND

This memorandum concerns a consult request of Nancy Scher, M.D., Medical Reviewer, DODP, regarding zoledronic acid-associated osteonecrosis. Interest in this adverse event was stimulated from a cluster of reports submitted to the FDA recently.

Additionally, Novartis Pharmaceuticals, the Sponsor for pamidronate and zoledronic acid, recently submitted a "Special Supplement-Changes Being Effected" to include a *Post-Marketing Experience* subsection of the *Adverse Reactions* section of Zometa's package insert to provide information on the adverse reaction as follows:

> *Cases of osteonecrosis (primarily of the jaws) have been reported [redacted]. Osteonecrosis of the jaws has [redacted] well documented multiple risk factors. [redacted] (e.g., chemotherapy, radiotherapy, corticosteroid), [redacted] co-morbid [redacted] (e.g., anemia, infection, pre-existing oral disease).*

Regarding their pharmacologic action, pamidronate and zoledronic acid are classified as bisphosphonates that act on the bone to inhibit resorption. As stated per the Sponsor's package inserts for both bisphosphonates, several factors are thought to contribute to this action, although their antiresorptive mechanism is not completely understood.[1,2] *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone.[1] Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. Hence, these actions interrupt the normal homeostasis of bone turnover and resorption.

LABELING

Currently, osteonecrosis is not labeled as an adverse reaction in neither Aredia's nor Zometa's package insert.

METHODS

Selection of Cases from AERS

An AERS database search was undertaken to determine the number of osteonecrosis cases associated with zoledronic acid and pamidronate use using the MedDRA High Level Term (HLT) Bone Disorders. Cases were included per physician diagnosis of osteonecrosis.

The data lock-points are from the date of marketing for the two bisphosphonates, October 31, 1991 for pamidronate and August 20, 2001 for zoledronic acid, until October 6, 2003.

RESULTS

Table 1 summarizes the characteristics of 53 zoledronic acid and pamidronate cases. These cases are presented in one table because their efficacy is linked to the same mechanism. Additonally, many patients received both bisphosphonates; thus, difficulty lies in classifying the cases according to bisphosphonate use as the half-lives of the bisphosphonates are long.[1,2]

Table 1. Demographics for Pamidronate and Zoledronic Acid Cases

Selected Characteristics	N=53
Approval date	
Pamidronate	10/31/1991
Zoledronic acid	8/20/2001
Reporting year	2001-2003
Country of origin	
Domestic	51
Foreign	2
Reporter	
Dentist	5
Oral surgeon	42
Oncologist	4
Healthcare professional	2
Age	N=47
Range (years)	40-82
Mean	65
Median	65
Sex	N=51
Female	34
Male	17
Cancer type	
Breast	19
Multiple myeloma	20
Chronic myelocytic leukemia	1
Colon	1
Prostate	3
Uterine	1
None	1
Unknown	6
Bisphosphonate treatment	
Pamidronate only	30
Zoledronic acid only	6
Pamidronate & zoledronic Acid	17
Reaction onset	
Pamdronate only	N=12
Range (days)	272-1722
Mean	981
Median	898
Zoledronic acid only	n=4
Range (days)	163-441
Mean	318
Median	333
Site of osteonecrosis	
Dental cavity	52
Femoral head	1

Table 1. Demographics for Pamidronate and Zoledronic Acid Cases (Continued)

Confounding factors*	N=39
Chemotherapy	20
Radiation	5
Steroids	16
Extraction	15
Bone marrow transplant	3
Treatment modalities	N=30
Debridement	3
Debridement with tooth extraction	1
Surgery (maxillectomy, mandibulectomy, or sequestrectomy)	23
Oral antral fistula	3
Outcome*	
Hospitalized	0
Death	0
Non-Serious	53
Not recovered	5

* Not mutually exclusive

Summary of Cases

A total of 53 cases, 30 with pamidronate use only, 6 with zoledronic acid use only, and 17 with both zoledronic acid and pamidronate use, were found in AERS. All cases, except for two, were domestic. No patients experienced serious sequelae resulting in hospitalization or death.

Because both medications are from the same therapeutic class and there was difficulty in determining the primary suspect drug, the cases are analyzed together. In cases in which patients received both bisphosphonates, all patients first received pamidronate prior to switching over to zoledronic acid.

Pertaining to patient demographics, the average patient age was elderly at 65 years, and the ratio of females to males was 2:1. For the two largest treatment groups, 20 (38%) patients received either bisphosphonate for osteolytic lesions secondary multiple myeloma and 19 ((36%) for bone metastases arising from breast cancer. Uterine, prostate, and colon cancers and chronic myelocytic leukemia comprised the remaining malignancies.

All reporters, except in four cases, were oral surgeons or dentists. With respect to their medical specialty, all cases, except for one, stated the site of osteonecrosis was the jaw. The one exception was a foreign case that described osteonecrosis of the femoral head. For the cases involving the jaw, the cases often came to the attention of an oral surgeon or dentist for nonhealing of bone following dental extractions. No cases mentioned dental caries as a cause of osteonecrosis.

As shown in Table 1, about three-quarters of the patients had received another treatment besides bisphosphonates, such as bone marrow transplant, chemotherapy, radiation, or steroids (dexamethasone and prednisone) for their cancer.

Only one patient in our case series received a bisphosphonate for a noncancerous indication, namely post-menopausal osteoporosis. This patient received treatment previously with alendronate.

Below are three index narratives, two pertain to osteonecrosis of the oral cavity and one to osteonecrosis of the femoral head:

<u>Index narrative: 4187827-9, Domestic</u>

A 72-year old female was placed on zoledronic acid (dose and frequency not specified) for postmenopausal osteoporosis on May 11, 2003 and developed osteonecrosis of the right mandible on August 20, 2003. Her diagnosis was confirmed through two biopsies, CT scan and X-ray. Restorative treatment consisted of multiple surgeries and antibiotic treatment and her care was ongoing at the time of the report. The patient had a wisdom tooth extraction and dental implants. Her medical history also included hypothyroidism which was treated with levothyronine, gastroesophageal reflux disease which was treated with esomeprazole, hyperlipidemia which was treated with simvastatin, and osteoarthritis for which treatment not stated. For osteoporosis, she has received alendronate, raloxifene, hormone replacement therapy, and salmon calcitonin.

<u>Index narrative 4148113-6, Domestic</u>

A 42-year old female started receiving pamidronate 90 mg (no frequency or stop date provided) for metastatic breast cancer in February 2000. After a dental extraction (date unspecified), the

patient failed to heal in December 2001, despite debridement and antibiotics. An examination by an oral surgeon revealed exposed bone of the right posterior mandible and reported osteonecrosis of the mandible. The patient was not treated with any radiation, but did receive steroid therapy (no dates, duration, or name of steroid were provided). In March 2002, she initiated treatment with zoledronic acid. As of May 19, 2003, the patient continued to have some numbness of the jaw and had trouble opening her mouth wide because of the numbness. Her other medications included anastrazole for breast cancer.

Index narrative 3830380-7, Foreign

A female patient of unknown age was treated with pamidronate 90 mg every four weeks since 1998 (exact date unspecified) for metastatic colon carcinoma. Her CT scan demonstrated normal findings of the femoral head "at this time". In June 2001, treatment was changed to zoledronic acid 4 mg every 4 weeks without any problems or adverse drug reactions. In November 2001, another CT scan revealed total necrosis of the femoral head. No other medical history or medications were stated.

DISCUSSION

Unlike most case series in which the cases were from numerous reporters, this case series was unique in that most of cases were reported by oral surgeons and dentists. One oral surgeon, in particular, submitted almost half of the cases in this review.[3] Another oral surgeon, who submitted several cases, recently published on this issue. Because of the reporter's occupation, the site of osteonecrosis detected in all cases, except for one, was the jaw. These cases often came to the attention of an oral surgeon or dentist for nonhealing of bone following dental extractions, exposed bone in oral cavity, osteomyelitis, chronic maxillary sinusitis secondary to necrotic bone, and fistulae of various types. Patients often complained of jaw pain, and upon presentation, the bone did not bleed when traumatized appropriately for diagnostic purposes. In some cases, necrotic bone was diagnosed based on radiographic, clinical, and histopathologic evidence. No mention of bone metastases as the cause of jaw pain was made.

It is interesting that the sites of osteonecrosis were in the oral cavity and were diagnosed by oral surgeons and dentists per complaints of jaw pain by patients in almost all of the cases. An explanation for this is that the oral cavity is the site most often exposed to the external environment via the teeth and oral mucosa.[3] With disturbance of the dental environment by periodontal inflammation, abscesses, and dental extractions, the rate of bone turnover increases as part of the repair process. Over one-third of these cases were a result of nonhealed dental extractions.

The sequelae of the osteonecrosis were severe in a number of cases. Once detected, treatment in all cases was necessary. In some cases, debridement or a course of antibiotics were sufficient to treat necrotic area, but many patients underwent extensive surgical procedures, such as resection of the mandible or maxilla, or sequestrectomy. In five cases that reported this information, the necrotic area still had not healed, presumably because of impaired bone turnover and resorption. The recovery time can be prolonged and painful as the half-lives of the bisphosphonates in the bone are long.[1,2]

Analysis of the osteonecrosis cases with zoledronic acid and pamidronate use suggests that there is a causal association between the adverse event in question and the medications, despite incomplete medical histories on the patients and confounders, such as radiation, chemotherapy,

and steroid use.[4,5,6] Although the etiologic cause may be multifactorial as almost all of these patients had cancer and received chemotherapy, radiation and steroids, the common denominator is that these patients were treated with bisphosphonates. These therapies can either impair the immune system response by increasing the risk for infection or disturb the integrity of the bone matrix.

Our one noncancerous case involving post-menopausal osteoporosis suggests that zoledronic acid and pamidronate may be causally associated with osteonecrosis. Not included in our analysis as it was communicated orally, one reporter, an oral surgeon, stated that he was aware of three patients, without malignancy and no receipt of chemotherapy, who experienced osteonecrosis associated with bisphosphonate use. Two patients received zoledronic acid treatment and one patient was administered alendronate. Although it is not discussed here, we have noted alendronate cases associated with osteonecrosis in our AERS database and we intend to review oral bisphosphonates for cases of osteonecrosis to determine whether this may be a drug class effect.

CONCLUSIONS

Our postmarketing data indicate a safety concern exists for zoledronic acid and pamidronate, in reference to osteoporosis, though there are confounders in these cases. The zoledronic acid and pamidronate labeling should be amended to note that there have been postmarketing cases of osteonecrosis associated with these medications. Additionally, the labeling should state that the recovery time can be prolonged, even after discontinuing the bisphosphonates as the half-lives are long. Prescribers should alert patients to report any jaw pain and once bone metastases is ruled out, referral to a dentist or oral surgeon for appropriate treatment is necessary.

We also intend to review oral bisphosphonates for cases of osteonecrosis to determine whether this may be a class effect.

Jennie T. Chang, Pharm.D.
Safety Evaluator

Lanh Green, R.Ph., M.P.H.
Team Leader

[1] Zometa product label. East Hanover, N.J.: Novartis Pharmaceuticals, 2002. (Accessed November 1, 2003, at http://www.us.zometa.com/info/about/index.jsp.)

[2] Aredia product label. East Hanover, N.J.: Novartis Pharmaceuticals, 2002. (Accessed November 1, 2003, at (http://www.pharma.us.novartis.com/products/name/aredia.jsp.)

[3] Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003 Sep;61(9):1115-7.

[4] Sung EC, Chan SM, Sakurai K, et al. Osteonecrosis of the maxilla as a complication to chemotherapy: a case report. Spec Care Dentist. 2002 Jul-Aug;22(4):142-6.

[5] Larson DL, Lindberg RD, Lane E, Goepfert H. Major complications of radiotherapy in cancer of the oral cavity and oropharynx. A 10 year retrospective study. Am J Surg. 1983 Oct;146(4):531-6.

[6] Mirzai R, Chang C, Greenspan A, Gershwin ME. The pathogenesis of osteonecrosis and the relationships to corticosteroids. J Asthma. 1999;36(1):77-95.

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/s/

Jennie Chang
11/24/03 01:19:31 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
11/24/03 02:56:54 PM
DRUG SAFETY OFFICE REVIEWER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennie Chang
1/8/04 04:13:48 PM
DRUG SAFETY OFFICE REVIEWER

Mark, Please re-sign as we could not find this
in DFS. Thanks. Jennie

Mark Avigan
1/9/04 01:47:00 PM
DRUG SAFETY OFFICE REVIEWER

Appendix 2: Chang 2004 FDA Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**ODS POSTMARKETING SAFETY REVIEW**	
TO: **Richard Pazdur, M.D., Director, Division of Oncology Drug Products (DODP), HFD-150**	**FROM:** **Jennie Chang, Pharm.D. , Safety Evaluator, Division of Drug Risk Evaluation (DDRE), HFD-430**	**ODS PID #** **D040283** **August 25, 2004**
DATE REQUESTED: May 6, 2004 **DATE RECEIVED: May 6, 2004**	**REQUESTOR/Phone #:** **Nancy Scher, M.D., DODP, HFD-150** **(301) 594-5745**	
DRUG (Est): Pamidronate, zoledronic acid, alendronate, risedronate	**NDA/IND #** **21-223, 20-036, 20-560, 20-835**	**SPONSOR**: **Novartis Pharmaceuticals, Merck, Proctor and Gamble Pharmaceuticals**
DRUG NAME (Trade): Aredia (pamidronate) and Zometa (zoledronic acid), Fosamax (alendronate), Actonel (risedronate)	**THERAPEUTIC CLASSIFICATION: Bisphosphonates**	
EVENT: Osteonecrosis and osteomyelitis		

Executive Summary:

This memorandum is an update of a consult that was completed on November 21, 2003 (see DFS for consult) by the Office of Drug Safety regarding osteonecrosis associated with two intravenous bisphosphonates, pamidronate and zoledronic acid.[1] Interest in this adverse event was stimulated from a cluster of reports submitted recently to FDA's postmarketing database in 2003. Additionally, Novartis Pharmaceuticals, the sponsor of zoledronic acid, submitted a "Special Supplement-Changes Being Effected" to include a *Post-Marketing Experience* subsection of the *Adverse Reactions* section of Zometa's package insert to provide information on osteonecrosis.

In this consult, we reviewed new cases of osteonecrosis associated with pamidronate and zoledronic acid that have been submitted since the previous consult. Osteomyelitis cases were included as a significant number of patients presented with a mixed osteonecrosis and osteomyelitis diagnosis. We also evaluated cases of osteonecrosis associated with oral bisphosphonates, namely alendronate and risedronate to determine if this is a therapeutic class effect.

Using the FDA's Adverse Event Reporting System database, a search was undertaken to determine the number of osteonecrosis cases associated with the four bisphosphonates using the MedDRA High Level Term (HLT) Bone Disorders. Cases were included per physician diagnosis of osteonecrosis and osteomyelitis. For pamidronate and zoledronic acid cases, the data lock-points are from October 6, 2003 (data termination point of the previous consult), until May 24, 2004. These cases that were analyzed during this time period were added to ones from the previous consult; thus, a cumulative review of the osteonecrosis cases is presented herein. The alendronate and risedronate cases were also reviewed for the time period from their marketing approvals, September 29, 1995 and March 27, 1998, respectively, until May 24, 2004.

As with the previous consult, the pamidronate and zoledronic acid cases were analyzed together because both bisphosphonates are indicated for the same patient population and most patients received the two bisphosphonates. In cases in which the patient received both bisphosphonates, all patients first received pamidronate prior to switching over to zoledronic acid, except for one patient who received two bisphosphonates on an alternating schedule.

A total of 139 cases, 47 (34%) with pamidronate use, 33 (24%) with zoledronic acid use, and 59 (42%) with both zoledronic acid and pamidronate use, were found in AERS. Less than ten percent of the cases were from foreign sources. For the oral bisphosphonates, 12 alendronate cases were related to osteonecrosis, and only one case was identified for risedronate. It should be noted that many cases did not provide complete information as to other confounding factors for osteonecrosis and osteomyelitis, treatment types for osteonecrosis and osteomyelitis, or outcomes.

Our search yielded mostly cases of osteonecrosis, but there was also a fraction (6%) of patients who had developed osteomyelitis secondary to pamidronate and zoledronic acid use and about one-quarter of the patients who had presented with a

mixed picture of osteomyelitis and osteonecrosis. For the alendronate and risedronate cases, all patients presented with osteonecrosis at time of diagnosis. Table 1 summarizes the characteristics of 139 zoledronic acid and pamidronate cases and Table 2 describes the osteonecrosis cases associated with alendronate use.

Since this issue was first reviewed, our update has identified more cases of osteonecrosis and osteomyelitis associated with pamidronate and zoledronic acid. Additionally, our AERS search has yielded osteonecrosis cases involving oral bisphosphonates, specifically alendronate and risedronate. The previous consult only focused on intravenous bisphosphonates.

Of interest, one reporter, an oral surgeon, provided us with a substantial number of cases associated with zoledronic acid and pamidronate use, which have since been published.[2] This same reporter submitted nine alendronate cases and the one risedronate case, all involving osteonecrosis of the jaw. As with the previous consult, most of the cases were submitted to us by oral surgeons.

Our postmarketing data indicate a safety concern exists for zoledronic acid and pamidronate, in reference to osteonecrosis, despite the confounders in these cases. It appears that osteonecrosis may be a class effect as exhibited by alendronate cases, in addition to zoledronic acid and pamidronate. Based on our recommendations from the previous consult[1], changes to the product label for zoledronic acid have been made to include language about osteonecrosis, but more language is necessary to highlight this adverse event because it is associated with the therapeutic class of bisphosphonates, as evidenced by our case analysis. This language should also be included in the other bisphosphonate product labels, namely those of alendronate, risedronate, and pamidronate. The case analysis of the intravenous bisphosphonates also revealed that some of the patients presented with a mixed diagnosis of osteomyelitis and osteonecrosis and in some cases, only osteomyelitis. Thus, language about this should be included in the *Post-Marketing Experience* subsection of the *Adverse Reactions*.

Search Date: From their respective marketing approval dates until May 24, 2004. The various marketing approval dates for the bisphosphonates are as follows:

alendronate	September 29, 1995
pamidronate	October 31, 1991
risedronate	March 27, 1998
zoledronic acid	October 6, 2003

Search Criteria: Using the AERS database, the following MedDRA term was applied: High Level Term (HLT) Bone Disorders. The cases were then individually reviewed and included in the analysis if a diagnosis of osteonecrosis was recorded.

Search Results:

A total of 139 cases, 47 (34%) with pamidronate use, 33 (24%) with zoledronic acid use, and 59 (42%) with both zoledronic acid and pamidronate use, were found in AERS. Less than 10% of the cases were from foreign sources. For the oral bisphosphonates, 12 alendronate cases pertained to osteonecrosis, and only one case was found for risedronate. It should be noted that many cases did not provide complete information as to other confounding factors for osteonecrosis, treatment types for osteonecrosis, or outcomes.

Intravenous Bisphosphonates: Pamidronate and zoledronic acid

Table 1 summarizes the characteristics of 139 zoledronic acid and pamidronate cases. Following the same format as the previous consult, these cases are presented in one table because their efficacy is linked to the same mechanism. Additionally, many patients received both bisphosphonates; thus, difficulty lies in classifying the cases according to bisphosphonate use as the half-lives of the bisphosphonates are long.[1,2] In cases in which patients received both bisphosphonates, all patients first received pamidronate prior to switching over to zoledronic acid, except for one case in which the patient alternated between zoledronic acid and pamidronate. A significant number of zoledronic acid and pamidronate cases were submitted, but the data collected by the sponsor was incomplete for a number of variables (see Novartis' briefing package submitted on June 21, 2004).

Pertaining to patient demographics for the pamidronate and zoledronic acid cases, the average patient age was 63 years, and the majority of the patients were of female gender. For the two largest treatment groups, 60 (43%) patients received either bisphosphonate for osteolytic lesions secondary multiple myeloma and 52 (37%) for bone metastases arising from breast cancer. Lung, uterine, prostate, and colon cancers, and chronic myelocytic leukemia comprised the other malignancies. Only one patient in our case series received a bisphosphonate for a noncancerous indication, which was post-menopausal osteoporosis. This patient received treatment previously with alendronate.

Slightly more than two-thirds of the patients were diagnosed with osteonecrosis and about one-quarter had a mixed diagnosis of osteomyelitis and osteonecrosis. Only six percent of the patients presented with osteomyelitis. The reaction onset in these patients extended past one year, with the duration of onset longer for pamidronate than zoledronic acid. The duration of onset of osteonecrosis and osteomyelitis was about six years for pamidronate and 14 months for zoledronic acid. For patients receiving both bisphosphonates, the average duration of reaction onset was over three years. Site of osteonecrosis/osteomyelitis was the jaw for all cases, except for one which was the femoral head.

Factors which may have contributed to osteonecrosis/osteomyelitis include chemotherapy, radiation, steroids, thalidomide, and bone marrow transplant. Over half of the patients received chemotherapy. Although 19 (14%) patients were radiated at their tumor site, only one patient was radiated in the jaw, specifically, the mandible. About half of the patients had received steroids.

Development of osteonecrosis/osteomyelitis occurred in 57 (41%) patients after a dental procedure consisting of a tooth extraction or root canal. Detection of osteonecrosis occurred after spontaneous tooth loss in four patients.

There were only five cases in which the patient reported as recovered from the event. Fourteen patients had improved outcomes, but had not fully recovered at the time of report. Two patients expired, but the cause of death was not stated in one case, which was reported by a foreign source. In the second case, one patient died from cardiac failure, not related to bisphosphonate treatment. For the remainder of the other cases, outcomes were not provided. The treatment modalities of osteonecrosis varied. Some patients received antibiotics and debridement, but others received more invasive types of treatment, including surgical resections, as shown in Table 1.

Oral bisphosphonates: Alendronate and Risedronate

The demographics and clinical characteristics of the alendronate cases are presented in Table 2. For risedronate, there was only one case reported. The AERS search yielded only one case of risedronate, it is presented below. For alendronate, 12 cases were identified, nine of which were from domestic sources and were reported by an oral surgeon who had treated these patients in his practice. This oral surgeon also identified a large number of pamidronate and zoledronic acid cases. Treatment indication for alendronate therapy was osteoporosis for all cases. All patients were elderly, as the average age was 70 years and most patients were of female gender. Outcomes and concomitant medications were not provided. Three-quarters of the patients received sequestrectomies for treatment of their osteonecrosis.

One osteonecrosis case involving risedronate was identified. An 80 year-old female had received risedronate (dose and duration, and outcome were not stated) for osteoporosis and subsequently developed necrotic bone of the left mandible following tooth extraction. Of note, the reporter is the same oral surgeon who reported all of the domestic alendronate cases.

Discussion:

This consult is an update of a prior consult; thus, please refer to the discussion points raised previously.[1]

Since this issue was first reviewed, our update has identified more cases of osteonecrosis associated with pamidronate and zoledronic acid. Additionally, our AERS search has identified osteonecrosis cases involving oral bisphosphonates, specifically alendronate and risedronate. The previous consult only focused on intravenous bisphosphonates. One reporter, an oral surgeon, submitted all nine domestic alendronate cases and one risedronate case, all involving osteonecrosis of the jaw. Of interest, this same reporter provided us with a substantial number of cases associated with zoledronic acid and pamidronate use, which have since been published.[2] As with the previous consult, most of the cases were submitted to us by oral surgeons.

The cases involving oral bisphosphonates suggest that this adverse event may be a class event, rather than limited to intravenous bisphosphonates. Despite the fact that in the majority of the cases, osteonecrosis was detected in the jaws and the cases were submitted by the same reporter, the common factor of alendronate treatment dismisses the idea that other variables may have influenced this adverse event. It should be noted that oral bisphosphonates are not as potent as the intravenous bisphosphonates, but they share the mechanism of action.

Although the issue involving the preponderance of the number of cases reported by oral surgeons and dentists was discussed in the prior consult, there remains a concern that reporter bias may affect the validity of the reports. The seriousness of the cases, along with the morbidity, does serve to discount this concern. Furthermore, we have received cases from other sources, such as dentists, oncologists, other oral surgeons. A fraction of these cases were also submitted by foreign reporters.

Conclusion:

Our postmarketing data indicate a continuing safety concern exists for the oral and intravenous bisphosphonates, despite the confounders in these cases. Based on our recommendations from the previous consult[1], changes to the product label for zoledronic acid have been made to include language about osteonecrosis, but more language is necessary to highlight this adverse event as this is associated with the therapeutic class of bisphosphonates, as evidenced by our case analysis. This language should also be included in the other bisphosphonate product labels, namely those of alendronate, risedronate, and pamidronate. The case analysis of the intravenous bisphosphonates also revealed that some of the patients presented with a mixed diagnosis of osteomyelitis and osteonecrosis and in some cases, only osteomyelitis. Thus, language about this should be included in the *Post-Marketing Experience* subsection of the *Adverse Reactions*.

Reviewer's Signature / Date:	
Team Leader's Signature / Date:	**Division Director's Signature / Date:**

Table 1. Demographics for Pamidronate and Zoledronic Acid Cases from Marketing Approval until May 24, 2004

Selected Characteristics	n=139
Approval date	
Pamidronate	10/31/1991
Zoledronic acid	8/20/2001
Reporting year	2001-2004
Geographic region of reporting source	
Domestic	120 (92%)
Foreign	19 (8%)
Age	N=132
Range (years)	34-88
Mean	63.2
Median	65
Gender	
Female	79 (57%)
Male	58 (42%)
Unknown	2 (1.4%)
Cancer type	
Breast[1]	52 (37%)
Multiple myeloma[3]	60 (43%)
Prostate	11 (8%)
Lung	2 (1%)
Chronic myelocytic leukemia	1
Colon	1
Lymphoma	1
Uterine	1
None	1
Unknown	9 (4%)
Diagnosis	
Osteonecrosis	97 (70%)
Osteomyelitis	9 (6%)
Mixed, osteomyelitis and osteonecrosis	33 (24%)
Bisphosphonate treatment	
Pamidronate only	47 (34%)
Zoledronic acid only	33 (24%)
Pamidronate & zoledronic Acid	59 (42%)
Reaction onset	
Pamidronate only (n=45)	n=23
Range, days	272-4211
Mean	2233
Median	2233
Zoledronic acid only (n=22)	n=14
Range, days	60-703
Mean	459
Median	441
Pamidronate and zoledronic acid together	n=34
Range, days	180-2433
Mean	1267
Median	1180
Site of osteonecrosis	
Jaw	138
Femoral head	1

[1] One patient had a concurrent diagnosis of ovarian cancer.
[2] One patient was receiving an experimental medication.
[3] One patient had a concurrent diagnosis of prostate cancer.

Table 1. Demographics for Pamidronate and Zoledronic Acid Cases (Continued)

Contributory factors*	
Chemotherapy	78 (56%)
Radiation[1]	19 (14%)
Steroids	67 (48%)
Thalidomide	17 (12%)
Bone marrow transplant	6 (4%)
Dental procedure leading to osteonecrosis	
Tooth extraction, root canal	57 (41%)
Spontaneous tooth loss	4 (3%)
Treatment modalities*	
Antibiotics	18 (13%)
Maxillectomy	6 (4%)
Debridement	15 (11%)
Oral surgery, unspecific	10 (7%)
Tooth extraction	10 (7%)
Sequestrectomy	9 (6%)
Mandibulectomy	9 (6%)
Oxygen	1
Oral antral fistula	3
Ostectomy	1
Root canal	2
Outcome*	
Improved	14
Recovered	5
Unknown	97
Not recovered	21
Death	2

* Not mutually exclusive

[1] Only one patient had radiation to the oral cavity (mandible).

Table 2. Demographics for Alendronate Cases[a]

Selected Characteristics	n=12
Approval date	9/29/1995
Reporting year	1997-2004
Country of origin	
Domestic	9
Foreign	3
Age	
Range (years)	59-82
Mean	70.3
Median	70
Gender	
Female	10
Male	2
Treatment indication	
Osteoporosis	12
Site of osteonecrosis	
Dental cavity	9
Femoral head	2
Vertebrae	1
Treatment modalities	
Sequestrectomy	9
Unknown	3
Concomitant medications	
Unknown	12
Outcome	
Unknown	11
Recovered	1

[a] One patient was also receiving zoledronic acid concomitantly.

cc: NDA 21-223, 20-036, 20-560, 20-835
HFD-150 Pazdur / Scher / Staten / Ibrahim
HFD-510 Orloff / Colman / Hedin / Stadel
HFD-430 Avigan / Chang / Green / Birdsong

[1] Chang J. Consult: Pamidronate- and zoledronic acid- osteonecrosis. DFS entry on November 21, 2003.

[2] Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 62:527-534, 2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennie Chang
1/31/05 03:01:44 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
2/1/05 11:00:11 AM
DRUG SAFETY OFFICE REVIEWER

Appendix 3: Pamer 2005 FDA Review

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: **August 9, 2005**

FROM: **Carol A. Pamer, R.Ph., Safety Evaluator**
Division of Drug Risk Evaluation, HFD-430

THROUGH: **Mark Avigan, M.D., C.M., Director**
Division of Drug Risk Evaluation, HFD-430

Rosemary Johann-Liang, M.D., Deputy Director
Division of Drug Risk Evaluation, HFD-430

TO: **David Orloff, M.D., Director**
Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510

SUBJECT: **Osteonecrosis and Osteomyelitis**
Drug: Alendronate (Fosamax & Fosamax Plus D)

PID#: **D050342**

*****CONFIDENTIAL: Contains proprietary IMS HEALTH drug utilization data. Data are not to be released to non-FDA employees without prior approval by IMS HEALTH.*****

EXECUTIVE SUMMARY

This consult provides a cumulative summary of cases of osteonecrosis or osteomyelitis (ON/OM) occurring at all anatomic sites that have been submitted to the AERS database for Fosamax (alendronate) from the time of U.S. approval in 1995 through May 24, 2005. A recent consult provided a cumulative summary for the 6 bisphosphonates marketed in the U.S.[1] Results of that consult were presented at a March 4, 2005 Oncologic Drugs Advisory Committee (ODAC) public meeting[2]. Since that public meeting and media coverage, additional cases have been reported.

AERS database searches identified a total of 47 unduplicated cases for alendronate. Most reports were from the United States (n= 30; 64%). The majority of reported cases involved the jaws (n=37; 79%). The largest proportion of patients were using alendronate for treatment of non-malignant skeletal disorders (n=30; 64%).

Many cases had conditions or a history of use of other drugs which were believed to be confounding factors present (n=32; 68%).

Patients in this case series experienced severely disabling symptoms and/or required multiple invasive medical interventions.

Revisions to the product prescribing information concerning osteonecrosis of the jaw(s) have been requested by HFD-510 for all bisphosphonates marketed in the U.S. and final labeling text has been developed.

I. Background and Introduction

Following the March 4, 2005 Advisory Committee meeting, additional cases of osteonecrosis and osteomyelitis have been submitted to the FDA AERS database in which the alendronate was indicated as the suspect drug. Three previous ODS consults have been completed regarding this adverse event for all bisphosphonates[3].

This consult provides a cumulative review of all reports for alendronate products in the AERS database through May 24, 2005 in which a specific diagnosis of osteonecrosis or osteomyelitis (ON/OM) was stated by the reporter. The primary interest is in cases of osteonecrosis of the jaw, although all AERS cases of this event occurring at any anatomic site were retrieved and reviewed.

II. Relevant Product Information

Alendronate was first approved for marketing in the U.S. in 1995.

Table 1: U.S. marketing status of alendronate-containing products

Generic Product Name NDA number(s) Brand name, NDA sponsor	Date of 1st U.S. Approval	Indications for Use	Dosage Forms
Alendronate sodium NDA 20-560, 21-575 Fosamax, Merck	9/29/1995	Treatment & prevention of osteoporosis in postmenopausal women; tx to increase bone mass in men with osteoporosis; tx of glucocorticoid-induced osteoporosis; tx of Paget's disease of bone.	5, 10, 35, 40, 70mg tablets; 70mg/75mL oral solution
Alendronate sodium and Cholecalciferol (Vit D) NDA 21-762 Fosamax Plus D, Merck	4/07/2005	Treatment of osteoporosis in postmeno-pausal women; tx to increase bone mass in men with osteoporosis	70mg alendronate/ 2800IU Vit D tablets

III. Drug Utilization Data

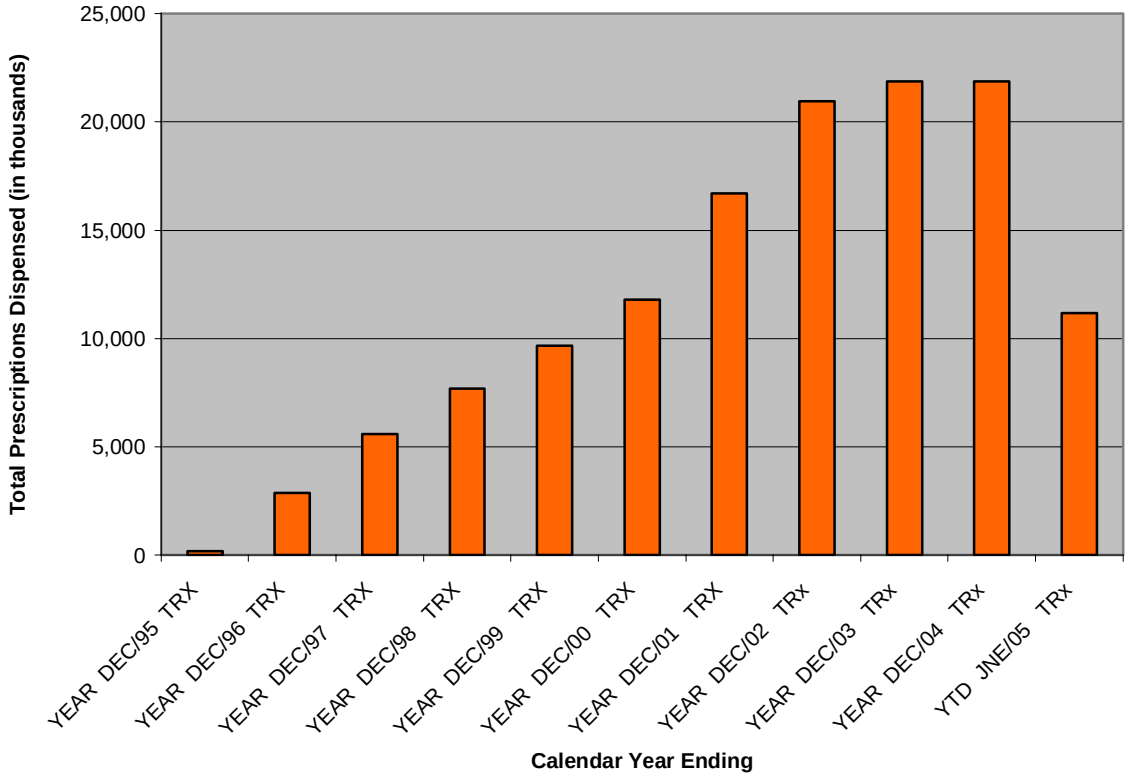
Figure 1 illustrates the volume of prescriptions that have been dispensed for alendronate-containing products per year, from 1995 through June 2005. IMS Health™ National Prescription Audit Plus was the source of these data[*].

NPA Plus measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected

[*] Data were prepared by Kendra Worthy, Pharm.D., Drug Utilization Data Specialist, Office of Drug Safety. Datasheets included the following: NPA Pamer D050342 Bisphosphonates 08-05-05 0508bisp.xls and NPA Chang 07-19-02 D020283 (alendronate 95-5.02.xls.

nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Figure 1: Total Prescriptions for Alendronate-Containing Products Dispensed by Retail Pharmacies (Source: IMS Health™ National Prescription Audit Plus)



IV. Pertinent Product Labeling Information

Currently, there is no mention of osteonecrosis or osteomyelitis of the jaw in the alendronate product labeling[4]. Revisions to the product prescribing information concerning osteonecrosis of the jaw(s) have been requested by HFD-510 for all bisphosphonates marketed in the U.S. and final labeling text has been developed.

V. Raw AERS data

An AERS database search was conducted, using the following search criteria:

Suspected drug product(s) included alendronat% as an active drug substance.

Reports were coded with at least one of the following 8 MedDRA PTs: ASEPTIC NECROSIS BONE, BONE INFECTION, OSTEOMYELITIS, OSTEOMYELITIS ACUTE, OSTEOMYELITIS BLASTOMYCES, OSTEOMYELITIS CHRONIC, OSTEOMYELITIS SALMONELLA, or OSTEONECROSIS.

As of May 24, 2005, this search of yielded a total of 46 reports, 45 of which reported a serious outcome, and one (1) reported a fatal outcome. Note that these represent raw AERS data counts and include duplicate reports and possible data entry or coding errors.

Table 2: Raw AERS counts for AERS database search, by specific MedDRA PT[†]

MedDRA PT	Raw AERS count
OSTEONECROSIS	25
ASEPTIC NECROSIS BONE	17
OSTEOMYELITIS	7
OSTEOMYELITIS ACUTE	1
BONE INFECTION, OSTEOMYELITIS BLASTOMYCES, OSTEOMYELITIS CHRONIC or OSTEOMYELITIS SALMONELLA	0

A previous extensive review for all bisphosphonates[5] retrieved six (6) additional cases in which Fosamax (alendronate) was listed as a Novartis "Medical History Product". Those 6 cases are also included in this analysis[‡], bringing the total raw count of reports reviewed to 54.

VI. Individual AERS case review

A. Case selection and exclusion

After the 54 reports were retrieved and reviewed individually and likely duplicate reports were combined, a total of 47 cases remained. Table 3 in Attachment 1 is a brief listing of the primary characteristics of these cases.

B. Summary of included cases

Descriptive statistics for case characteristics were calculated and summarized in tabular format. Table 4 summarizes characteristics for cases in which alendronate was the only bisphosphonate reported. Table 5 provides a summary of characteristics for cases in which current or a history of one or more other bisphosphonate was mentioned, in addition to alendronate.

1. Cases in which alendronate was the only bisphosphonate mentioned

Thirty eight (38) cases were reported in which alendronate was the only bisphosphonate mentioned. The jaw(s) were the affected site(s) in 28 of 38 reports. For cases affecting the jaw, osteonecrosis only was reported in 18 cases, both osteonecrosis and osteomyelitis in 5 cases, and osteomyelitis only in 5 cases.

Most patients were female (31 of 36), where patient gender was known. The mean age of all patients was 71.6 years (n= 33; SD = 10.1).

The indications for use of alendronate were primarily chronic skeletal disorders: osteoporosis (n=22), osteoporosis w/history of lung cancer (n=1), "osteopenia" (n=2), and osteitis deformans (n=1). Indication for use was not known 12 cases.

[†] Six (6) additional cases from previous bisphosphonate case review are NOT included in these raw counts.
[‡] AERS case numbers: 3989691, 4103044, 4117226, 4151969, 4191724, and 5695687.

The average daily dose of alendronate in most cases was 10mg (n = 20). Dose was unknown in 16 cases.

In many of the reports, time to onset of osteomyelitis or osteonecrosis of the jaw (OMJ/ONJ) was not easily ascertained, which may also be a reflection of the nature of the condition. For example, some patients began to have jaw pain or loosened teeth prior to diagnosis of OMJ/ONJ. These symptoms preceded other, more severe symptoms which required treatment with root canals, tooth extraction (often with non-healing of the extraction site), mandibulectomy, sequestrectomy, prolonged antibiotic therapy, debridements, hyperbaric oxygen therapy, etc. Detailed dosing information was often incomplete as well. Because of this, total cumulative duration of use of alendronate was calculated, in calendar months' of time, rather than time to onset of the condition. For 22 cases in which alendronate was the only bisphosphonate mentioned and the duration of use was known, the mean cumulative duration of use was 54.5 months.

The majority of cases reported at least one of the specified risk factors (n = 24). Seven (7) of the 14 cases with no risk factors mentioned were reports in which the jaw was affected[§]. Two (2) of the cases were published case reports. The reporter in these 2 cases mentioned that the patient had no history of malignancy or chemotherapy. Otherwise, extensive information on the patient medical and medication histories was not provided for the 7 reports.

Alendronate was known to be discontinued in 16 of 38 cases. In eight (8) cases, the adverse events continued after alendronate was stopped. Of 7 cases in which it was stated that alendronate was continued, 3 patients were reported to recover. In 15 reports, it was not known if the drug was discontinued.

One (1) fatality was reported (AERS case 5697067). The patient died due to preexisting lung cancer, although symptoms of osteonecrosis of the jaw persisted until the time of death.

[§] AERS case numbers: 4137140, 4137143, 5679302, 5753325, 5753327, 5795388, 5800437.

Table 4: Cases in which alendronate was the ONLY bisphosphonate mentioned, current or history of (n=38)

Adverse event(s) reported	Count
Osteonecrosis Jaw	18
Osteonecrosis Non-Jaw	10
Osteomyelitis Jaw	5
Osteomyelitis &Osteonecrosis Jaw	5

Indication(s) for use	Count
Osteoporosis	22
Unknown	12
Osteopenia	2
Osteitis Deformans	1
Osteoporosis, Lung Cancer	1

Country of reporter	Count
United States	22
Australia	3
Switzerland	3
Germany	3
France	2
Great Britain	2
South Africa	2
Singapore	1

Risk factors present*	Count
Cases with **no** risk factors mentioned	14
Tooth extraction or dental implant manipulation	12
Corticosteroid use	11
Cancer chemotherapy	3
Radiotherapy	1
Thalidomide	0
Bone marrow or stem cell transplant	0

Daily dose of alendronate (mg)	
10 mg	20
5 mg	1
40 mg	1
Unknown	16

Age of patient (years) (n=33)	
Mean	71.6
Standard Deviation	10.1
Median	71.0
Range	47.0 to 97.0

Cumulative duration of use (months) (n = 22)	
Mean	54.5
Standard Deviation	32.1
Median	57.5
Range	2.5-125.0

Gender of patient	Count	Proportion
Female	31	0.82
Male	5	0.13
Not specified	2	0.05

Intervention(s)†	Count
Surgery	23
Hospitalization	14
Non-surgical interventions (debridement, antibiotics, hyperbaric oxygen, antiseptic rinses)	14

Outcome, according to drug continuance	Drug not DC	Unk if drug DC	Drug DC	Total
Condition ongoing	2	4	8	**14**
Patient recovered	3	3	7	**13**
Unknown patient status	2	8	1	**11**
Total	**7**	**15**	**16**	**38**

* Not mutually exclusive. More than one risk factor per case may be counted.
† Not mutually exclusive. More than one intervention per case may be counted.

2. Cases in which alendronate and use of another bisphosphonate was mentioned

Nine (9) reports were received in which the patient had a history of use of alendronate and at least one other bisphosphonate. Characteristics of those cases are briefly summarized in Table 5.

Table 5: Cases in which alendronate and ONE OR MORE bisphosphonate was mentioned, current or history of (n=9)

Adverse event(s) reported	Count
Osteonecrosis Jaw	4
Osteomyelitis &Osteonecrosis Jaw	3
Osteomyelitis Jaw	2
Osteonecrosis Non-Jaw	0

Indication(s) For Use	Count
Osteoporosis	4
Breast Cancer	2
Bone Lesion Breast Cancer	1
Osteopenia Breast Cancer Ovarian Cancer	1
Osteopenia Prostate Cancer	1

Bisphosphonates mentioned	
Alendronate Icadronate Pamidronate	1
Alendronate Pamidronate	1
Alendronate Pamidronate Zoledronic acid	3
Alendronate Zoledronic acid	3
Risedronate Alendronate	1

Risk factors present[‡]	Count
Cases with **no** risk factors mentioned	1
Corticosteroid use	2
Tooth extraction or dental implant manipulation	6
Cancer chemotherapy	5
Radiotherapy	1
Thalidomide	0
Bone marrow or stem cell transplant	1

Age of patient (years) (n=9)	
Mean	70.1
Standard Deviation	8.6
Median	72.0
Range	59.0-83.0

Gender of patient	
Female	8
Male	1

Country of reporter	Count
United States	8
Japan	1

Intervention(s)[†]	Count
Non-surgical interventions (debridement, antibiotics, hyperbaric oxygen, antiseptic rinses)	7
Surgery	6
Hospitalization	2

Outcome, according to drug continuance

	Drug not DC	Unk if drug DC	Drug DC	Total
Condition ongoing	3	1	3	**7**
Patient recovered	0	0	1	**1**
Unknown status	0	1	0	**1**
Total	**3**	**2**	**4**	**9**

[‡] Not mutually exclusive. More than one risk factor per case may be counted.

VII. Summary

This consult provides a cumulative summary of all cases of osteonecrosis or osteomyelitis (ON/OM) that have been submitted to the AERS database for Fosamax (alendronate), from time of U.S. marketing in 1995 through May 24, 2005. Currently, there is no mention of osteonecrosis or osteomyelitis of the jaw in the product labeling[6]. Revisions to the product prescribing information concerning osteonecrosis of the jaw(s) have been requested by HFD-510 for all bisphosphonates marketed in the U.S. and final labeling text has been developed.

Carol A. Pamer, R.Ph.
Safety Evaluator
Division of Drug Risk Evaluation [DDRE]

Concur:

Lanh Green, Pharm.D., M.P.H.
Safety Evaluator Team Leader, DDRE

ATTACHMENT 1 Table 3: Cases included in summary (n=47)

AERS CASE NUMBER	AGE	SEX	MFR CNTRL NO.	AE **	ALL REACTIONS	INDICATION	DRUG(S) PRESCRIBED	Rx DC††	ON/RE/U‡‡
5734991	67	F	US-MERCK-0502USA00754	OMJ	OMJ: OSTEOMYELITIS TOOTH DISORDER	UNKNOWN	FOSAMAX	Y	ON
5753325	U	F	US-MERCK-0503USA00475	OMJ	OMJ: OSTEOMYELITIS	UNKNOWN	FOSAMAX	U	U
5753330	60	F	US-MERCK-0503USA00474	OMJ	OMJ: OSTEOMYELITIS	UNKNOWN	FOSAMAX	U	ON
5757724	U	F	DE-MERCK-0503DEU00064	OMJ	OMJ: OSTEOMYELITIS BONE DISORDER FISTULA NASOPHARYNGITIS SINUSITIS SEQUESTRECTOMY	OSTEOPOROSIS	FOSAMAX INSULIN	U	ON
5795388	83	F	CH-MERCK-0505CHE00005	OMJ	OMJ: OSTEOMYELITIS ACUTE	OSTEOPOROSIS	FOSAMAX CALCIUM VIT D AMILORIDE HCTZ TRAMADOL MIDAZOLAM	N	U
4117226	65	M	PHEH2004US03404	OMJ	OMJ: TOOTH EXTRACTION AMNESIA ANAEMIA OF CHRONIC DISEASE BONE DEBRIDEMENT ERECTILE DYSFUNCTION HOT FLUSH HYPERCHOLESTEROLAEMIA IMPAIRED HEALING LIBIDO DECREASED OSTEOMYELITIS OSTEOPENIA PAIN PERINEAL PAIN TOOTH INFECTION	OSTEOPENIA PROSTATE CANCER	FOSAMAX & AREDIA & ZOMETA LUPRON HYDROCORTISONE CELEBREX TAMOXIFEN TRAZODONE NIZORAL AVODART CASODEX	N	ON
5695687	83	F	CTU 233980	OMJ	OMJ: MALNUTRITION OSTEOMYELITIS	BREAST CANCER	FOSAMAX & AREDIA & ZOMETA	N	ON
5697065	83	F	US-MERCK-0412USA01020	OMJ ONJ	OMJ/ONJ: HIP FRACTURE THROMBOSIS ASEPTIC NECROSIS BONE IMPLANT SITE INFECTION NASAL DISORDER REGURGITATION OF FOOD	OSTEOPOROSIS	FOSAMAX SYNTHROID COUMADIN CHEMO NOS	N	ON
5718835	67	F	AU-MERCK-0501AUS00109	OMJ ONJ	OMJ/ONJ: ASEPTIC NECROSIS BONE OSTEONECROSIS FISTULA OSTEOMYELITIS TOOTH LOSS	UNKNOWN	FOSAMAX PREDNISOLONE LEFLUNOMIDE ACETAMINOPHEN APAP W/CODEINE TRAMADOL CELECOXIB ESOMEPRAZOLE ROXITHROMYCIN	U	ON

** OMJ = Osteomyelitis of the jaw; ONJ = Osteonecrosis of the jaw; ON OT = Osteonecrosis at non-jaw site. (Note: Primary sort column for this table.)
†† Rx DC = Bisphosphonate(s) reported to be discontinued. Y = Yes, drug(s) were discontinued; N = No, drug(s) were continued; and U = Unknown if drug(s) were discontinued.
‡‡ ON/RE/U = Outcome of condition as of last known follow-up. ON = Adverse events were ongoing or not reported as completely recovered; RE = Reported as completely recovered; and U = Unknown outcome.

AERS CASE NUMBER	AGE	SEX	MFR CNTRL NO.	AE **	ALL REACTIONS	INDICATION	DRUG(S) PRESCRIBED	Rx DC††	ON/RE/U‡‡
5725134	59	F	US-MERCK-0410USA04001	OMJ ONJ	OMJ/ONJ: TOOTH ABSCESS ARTHRALGIA PAIN IN EXTREMITY BLADDER DISORDER CLOSTRIDIUM COLITIS CROHN'S DISEASE SYNCOPE OSTEONECROSIS TEMPOROMANDIBULAR JOINT SYNDROME BODY HEIGHT DECREASED GASTROINTESTINAL HAEMORRHAGE OESOPHAGEAL CANDIDIASIS ANAEMIA SICCA SYNDROME OSTEOMYELITIS	OSTEOPENIA	FOSAMAX NEURONTIN OXYCODONE OXYCONTIN VIOXX AZATHIOPRINE PREDNISONE PLAQUENIL PROZAC	Y	ON
5753327	U	U	US-MERCK-0503USA00695	OMJ ONJ	OMJ/ONJ: OSTEOMYELITIS OSTEONECROSIS	UNKNOWN	FOSAMAX	U	U
5754921	74	F	GB-MERCK-0503GBR00070	OMJ ONJ	OMJ/ONJ: OSTEONECROSIS OSTEOMYELITIS	OSTEOPOROSIS	FOSAMAX PYRIDOSTIGMINE OMEPRAZOLE LETROZOLE APAP ALBUTEROL DIHYDROCODEINE PREDNISOLONE	Y	ON
4103044	75	F	PHEH2004US02447	OMJ ONJ	OMJ/ONJ: JAW OPERATION OSTEOMYELITIS ABSCESS JAW ABSCESS SOFT TISSUE ACTINOMYCOSIS ALVEOLOPLASTY ATRIAL FIBRILLATION ERYTHEMA EXCESSIVE GRANULATION TISSUE EYE PAIN FISTULA GINGIVITIS INFECTION INFLAMMATION NECK PAIN ORAL INFECTION	BREAST CANCER	FOSAMAX & AREDIA & ZOMETA TAMOXIFEN ARIMIDEX VIOXX NEXIUM REGLAN ATIVAN OXYCONTIN ACEON	Y	ON
4151969	80	F	CIP04001052	OMJ ONJ	OMJ/ONJ: IMPAIRED HEALING ISCHAEMIA JAW DISORDER OPEN WOUND OSTEOMYELITIS CHRONIC OSTEONECROSIS PAIN IN JAW POST PROCEDURAL COMPLICATION PURULENT DISCHARGE SWELLING VASCULAR INSUFFICIENCY	OSTEOPOROSIS	ACTONEL& FOSAMAX INFLIXIMAB	Y	RE
4191724	59	F	PHEH2004US08275	OMJ ONJ	OMJ/ONJ: SWELLING SURGERY PAIN OSTEOMYELITIS SINUS DISORDER OSTEONECROSIS WOUND DEBRIDEMENT TOOTH EXTRACTION	OSTEOPENIA BREAST CANCER OVARIAN CANCER	FOSAMAX & ZOMETA NAVELBINE COUMADIN FAMVIR NEXIUM EVISTA DETROL TRAZODONE CLONAZEPAM CELEXA NITROFURANTOIN "STEROID" CHEMO, OTHER	Y	ON
4137140	59	F	US-MERCK-0404USA02620	ONJ	ONJ: OSTEONECROSIS [JAW]	OSTEOPOROSIS	FOSAMAX	U	U
4137141	82	F	US-MERCK-0404USA02618	ONJ	ONJ: OSTEONECROSIS [JAW]	OSTEOPOROSIS	FOSAMAX	U	RE
4137143	60	F	US-MERCK-0404USA02621	ONJ	ONJ: OSTEONECROSIS [JAW]	OSTEOPOROSIS	FOSAMAX	U	RE

AERS CASE NUMBER	AGE	SEX	MFR CNTRL NO.	AE **	ALL REACTIONS	INDICATION	DRUG(S) PRESCRIBED	Rx DC††	ON/RE/U‡‡
4137144	77	F	US-MERCK-0404USA02400	ONJ	ONJ: OSTEONECROSIS [JAW]	OSTEOPOROSIS	FOSAMAX PREDNISONE	Y	RE
4137155	68	F	US-MERCK-0404USA02622	ONJ	ONJ: OSTEONECROSIS	OSTEOPOROSIS	FOSAMAX ESTROGENS	U	RE
4146582	97	M	SG-MERCK-0404SGP00001	ONJ	ONJ: FEMORAL NECK FRACTURE CHOLECYSTITIS ACUTE ASEPTIC NECROSIS BONE [JAW] EXOSTOSIS SINUSITIS CHOLELITHIASIS TOOTH EXTRACTION	OSTEOPOROSIS	FOSAMAX COZAAR CALCIUM ATORVASTATIN PROSCAR ALFUZOSIN	Y	RE
5679302	68	F	US-MERCK-0410USA00021	ONJ	ONJ: FISTULA [ORAL] OSTEONECROSIS IMPAIRED HEALING	OSTEOPOROSIS	FOSAMAX COUMADIN KLONOPIN NIASPAN	Y	ON
5697067	71	F	US-MERCK-0412USA01021	ONJ	ONJ: LUNG NEOPLASM MALIGNANT OSTEONECROSIS [Death]	OSTEOPOROSIS; HX LUNG CANCER	FOSAMAX	Y	ON
5697073	59	F	US-MERCK-0410USA02228	ONJ	ONJ: ASEPTIC NECROSIS BONE, APHTHOUS STOMATITIS HERPES ZOSTER MOUTH ULCERATION	OSTEOPOROSIS	FOSAMAX PREMARIN PROMETRIUM TRAZODONE METHOTREXATE PREDNISONE ENBREL VITAMINS CALCIUM VIT D FOLIC ACID ANSAID	Y	RE
5699229	82	F	CTU 234464	ONJ	ONJ: IMPAIRED HEALING OSTEONECROSIS WOUND	OSTEOPOROSIS	FOSAMAX	U	ON
5750713	61	F	US-MERCK-0502USA03031	ONJ	ONJ: OSTEONECROSIS MEDICAL DEVICE COMPLICATION PALATAL DYSPLASIA	OSTEOPENIA	FOSAMAX COZAAR NORVASC POTASSIUM NEXIUM LASIX	Y	RE
5775884	70	F	GB-MERCK-0504GBR00068	ONJ	ONJ: OSTEONECROSIS	UNKNOWN	FOSAMAX ASA INSULIN LACTULOSE PREDNISOLONE DILTIAZEM QUININE METFORMIN EPOETIN LANSOPRAZOLE DOXAZOSIN AMITRIPTYLINE CITALOPRAM SIMVASTATIN LISINOPRIL CALCIUM BETAHISTINE FUROSEMIDE MORPHINE	Y	ON
5777372	84	F	CH-MERCK-0504CHE00024	ONJ	ONJ: OSTEONECROSIS OSTEITIS	UNKNOWN	FOSAMAX METHOTREXATE PREDNISONE LEVOTHYROXINE ALLOPURINOL DICLOFENAC	N	RE
5777387	81	F	CH-MERCK-0504CHE00023	ONJ	ONJ: OSTEONECROSIS OSTEITIS POST PROCEDURAL COMPLICATION	OSTEOPOROSIS	FOSAMAX AMIODARONE ASA TORSEMIDE MIDAZOLAM DICLOFENAC APAP W/CODEINE	N	RE
5780349	83	F	CTU 246109	ONJ	ONJ: OSTEONECROSIS	UNKNOWN	FOSAMAX PREDNISONE LOVASTATIN CALCITRIOL	Y	U

AERS CASE NUMBER	AGE	SEX	MFR CNTRL NO.	AE **	ALL REACTIONS	INDICATION	DRUG(S) PRESCRIBED	Rx DC††	ON/RE/U‡‡
5780396	73	M	AU-MERCK-0504AUS00157	ONJ	ONJ: ASEPTIC NECROSIS BONE BONE PAIN TOOTH DISORDER	OSTEITIS DEFORMANS	FOSAMAX AMLODIPINE TRAMADOL PERINDOPRIL	Y	RE
5795387	77	F	US-MERCK-0505USA01259	ONJ	ONJ: OSTEONECROSIS BETA HAEMOLYTIC STREPTOCOCCAL INFECTION BRAIN ABSCESS ABSCESS TOOTH DISORDER	OSTEOPOROSIS	FOSAMAX	Y	ON
5800437	66	M	US-MERCK-0505USA02015	ONJ	ONJ: OSTEONECROSIS	OSTEOPOROSIS	FOSAMAX	Y	RE
5761291	66	F	JP-MERCK-0503USA02487	ONJ	ONJ: OSTEONECROSIS	BONE LESION BREAST CANCER	FOSAMAX (IV) AREDIA ICADRONATE CYCLOPHOSPHAMIDE TEGAFUR URACIL FARMORUBICIN	N	ON
5748576	59	F	US-MERCK-0502USA02687	ONJ	ONJ: ASEPTIC NECROSIS BONE BONE DENSITY DECREASED BONE DISORDER DRUG EFFECT DECREASED DRUG INEFFECTIVE GASTROINTESTINAL DISORDER PERIODONTAL DISEASE TOOTH DEPOSIT	OSTEOPOROSIS	FOSAMAX AREDIA CALCIUM MVI LEVOTHYROXINE CLONAZEPAM SIMVASTATIN FIORICET FLEXERIL METHADOSE TIZANIDINE IRON ALBUTEROL APAP	Y	ON
3989691	72	F	PHEH2003US07453	ONJ	ONJ: DENTAL PROSTHESIS USER OSTEONECROSIS [JAW] BONE DEBRIDEMENT TOOTH EXTRACTION	OSTEOPOROSIS	FOSAMAX & ZOMETA CALCIUM VITAMIN D SIMVASTATIN NEXIUM SYNTHROID "HORMONES" E-VISTA MIACALCIN	U	ON
4137138	72	F	US-MERCK-0404USA02619	ONJ	ONJ: OSTEONECROSIS	OSTEOPOROSIS	FOSAMAX & ZOMETA	U	U
3821598	47	F	WAES 0207DEU00174	ON OT	ON FEMUR: ASEPTIC NECROSIS BONE [FEMUR] BONE DENSITY DECREASED FEMORAL NECK FRACTURE	OSTEOPOROSIS	FOSAMAX CALCIUM VITAMIN D ALPROSTADIL FLUORIDE PREDNISOLONE AZATHIOPRINE	U	U
5564889	68	F	WAES97046096	ON OT	ON HIP: BONE PAIN OSTEONECROSIS [HIP]	OSTEOPOROSIS	FOSAMAX CALCIUM VITAMIN D CIPROFIBRATE DIACERHEN	N	U
5654810	U	F	ZA-MERCK-0410ZAF00035	ON OT	ON FEMUR: ASEPTIC NECROSIS BONE [FEMUR]	UNKNOWN	FOSAMAX	U	U
5654813	U	U	ZA-MERCK-0410ZAF00036	ON OT	ON HIP: ASEPTIC NECROSIS BONE [HIP]	UNKNOWN	FOSAMAX	U	U
5671546	73	F	US-MERCK-0410USA01796	ON OT	ON FEMUR: ASEPTIC NECROSIS BONE [FEMUR]	OSTEOPOROSIS	FOSAMAX CALCIUM CITRATE VITAMIN D MAGNESIUM FOLIC ACID PYRIDOXINE ASCORBIC ACID VITAMINS TRIAMTERENE HYDROCHLOROTHIAZIDE	N	RE

AERS CASE NUMBER	AGE	SEX	MFR CNTRL NO.	AE **	ALL REACTIONS	INDICATION	DRUG(S) PRESCRIBED	Rx DC††	ON/RE/U‡‡
5690964	75	F	DE-MERCK-0410DEU00728	ON OT	ON FEMUR: ASEPTIC NECROSIS BONE [FEMUR]	OSTEOPOROSIS	FOSAMAX VITAMIN D CALCIUM DIHYDRALAZINE SULFATE LEVOTHYROXINE METILDIGOXIN CAPTOPRIL	N	ON
5794995	70	F	US-MERCK-0505USA01263	ON OT	ON: ASEPTIC NECROSIS BONE [FEMUR]	OSTEOPOROSIS	FOSAMAX ESTROGENS	Y	ON
3064414 3156967	79	F	WAES 97096074	ON OT	ON VERTEBRAE: BACK PAIN OSTEONECROSIS [VERTEBRAE]	OSTEOPOROSIS	FOSAMAX COZAAR DOMPERIDONE MORPHINE NADROPARIN NICARDIPINE THIORIDAZINE	Y	RE
4094536 4119791	67	M	US-MERCK-0402USA01370 WAES 0402USA01370	ON OT	ON FEMUR: ASEPTIC NECROSIS BONE [FEMUR] FALL FOOT FRACTURE MULTIPLE FRACTURES FEMORAL NECK FRACTURE RIB FRACTURE BODY HEIGHT DECREASED INTERVERTEBRAL DISC DISORDER PUBIC RAMI FRACTURE SPINAL DEFORMITY	UNKNOWN	FOSAMAX LANOXIN PREVACID IMODIUM PREDNISONE PROGESTERONE TESTOSTERONE COUMADIN	U	U
3538520 3531491 3535892 3541943	73	M	WAES 00093492 B0087552A 20000800757 2000-08-1715	ON OT	ON FEMUR: ASEPTIC NECROSIS BONE [FEMUR]	UNKNOWN	FOSAMAX VENTOLIN FLOVENT THEOPHYLLINE IPRATROPIUM BUDESONIDE MULTIVITAMIN PREDNISOLONE	U	U

[1] Carol Pamer and Carolyn McCloskey, Osteonecrosis and Osteomyelitis [with] Alendronate (Fosamax), Etidronate (Didronel), Pamidronate (Aredia & generic products), Risedronate (Actonel), Tiludronate (Skelid), and Zoledronic acid (Zometa) ODS Project ID D040847 (April 15, 2005)

[2] http://www.fda.gov/ohrms/dockets/ac/cder05 html#OncologicDrugs

[3] Jennie Chang, ODS Project IDs D030552 (November 21, 2003) and D040283 (August 25, 2004). Carol Pamer and Carolyn McCloskey, ODS Project ID D040847 (April 15, 2005).

[4] Merck & Co., Inc. Fosamax Plus D™ (alendronate sodium/cholecalciferol) tablets Complete Prescribing Information. Approval date 4/7/2005

[5] ODS Project ID D040847: Carol Pamer & Carolyn McCloskey, April 15, 2005.

[6] Merck & Co., Inc. Fosamax Plus D™ (alendronate sodium/cholecalciferol) tablets Complete Prescribing Information. Approval date 4/7/2005

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/s/

Carol Pamer
8/9/05 01:16:21 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
8/10/05 05:07:04 PM
MEDICAL OFFICER

Appendix 4: McCloskey 2011 FDA Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 11, 2011, Abridged July 29,2011 (removed Appendices & corrected the text and endnotes accordingly)
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic Products (DRUP) Office of Drug Evaluation III, CDER
Through:	Solomon Iyasu, MD, MPH, Director Division of Epidemiology I (DEPI I) Office of Surveillance and Epidemiology (OSE), CDER Judy Staffa, RPh, PhD, Director Division of Epidemiology II (DEPI II), OSE Kate Gelperin, MD, MPH, Acting Epidemiology Team Leader DEPI I, OSE
From:	Carolyn A. McCloskey, MD, MPH, Epidemiologist PROBE Scientific Team Leader, DEPI I, OSE
Subject:	Summary of Epidemiology Contract Study: Oral Bisphosphonates and Osteonecrosis of the Jaw at Kaiser Permanente Northern California; also called the Predicting Risk of Osteonecrosis with Bisphosphonate Exposure (PROBE) Study
Drug Name(s):	Fosamax (alendronate sodium), Actonel (risedronate sodium), and Boniva (ibandronate sodium) Class: Oral Bisphosphonates (OBP)
OSE RCM #:	RCM #2006-1012

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CONTENTS

1 INTRODUCTION & BACKGROUND

To obtain safety information on drug products, FDA contracts with external healthcare groups to conduct pharmacoepidemiologic studies. The purpose of such studies is to quantify and characterize risk for particular adverse events associated with specific drug therapies. This review summarizes a study on oral bisphosphonate (OBP) use and risk for osteonecrosis of the jaw (ONJ) conducted by FDA in collaboration with Kaiser Permanente of Northern California (KPNC). FDA contracted with KPNC in 2006 to study OBPs and ONJ in response to published studies on intravenous bisphosphonates (IVBP) associated with ONJ, and the concern that ONJ may also be associated with OBP which are indicated for the treatment or prevention of osteoporosis and are widely prescribed to healthy postmenopausal women. The OBP exposure in the US was approximately 5.4 million persons in 2007, almost 5.7 million in 2008, and almost 5.2 million in 2009[1] (retail pharmacy data, not including mail order prescriptions). The study was named PROBE (Predicting Risk of Osteonecrosis with Bisphosphonate Exposure study). Determination of the prevalence of ONJ among patients using chronic OBPs was the focus of phase I of the study. Phase II focused on examining other possible risk factors and effect modifiers for development of ONJ. This review provides FDA comments on the study as well as thoughts on ways to use the information from this study in FDA's mission of protecting the health of Americans.

FDA initially discussed the feasibility of evaluating OBPs and ONJ with Joe Selby, MD, at KPNC. Once it was agreed to undertake the study, FDA worked closely with Joan Lo, MD, the KPNC principal investigator, and her team for the duration of this study. The FDA scientific team for phase I (ONJ prevalence determination) included Carolyn McCloskey (FDA Scientific Team Leader), Mary Willy, and Judy Staffa. For phase II (risk factor analyses), the FDA scientific team included Carolyn McCloskey (FDA Scientific Team Leader), David J. Graham, Antonio Paredes, Audrey Gassman, and Marty Kaufman.

2 METHODS

The PROBE study, a cross sectional study, involved surveying adult members of KPNC in 2007 who had received at least a year of prescriptions for OBPs. The survey focused on the status of their teeth and gums and included demographic and past medical history questions framed from published information on ONJ such as the duration of OBP prior to ONJ. Most patients (99%) had alendronate exposure with a few patients exposed to risedronate and ibandronate. This is similar to drug utilization patterns for OBPs in the US overall where alendronate (~60%) is the market leader[1]. Patients reporting potential gum symptoms were contacted by telephone and invited for an oral examination. The study captured health information from reviewing healthcare records, surveying patients for additional information, and from oral examinations when indicated. The prevalence study methods and results (phase I) are published[2].

Data from phase I (survey, healthcare records, and oral exams) were evaluated for ONJ risk factors in phase II. The PROBE study cohort had at least one year of OBP exposure with a subset of patients with oral or dental symptoms who were examined or had their dental records reviewed.

Cases of ONJ, "ONJ-like", and Stage 0 disease were identified within the subset of survey responders with oral or dental symptoms. Definitions of the following outcomes are:

- Bisphosphonate-related osteonecrosis of the jaw (BRONJ) per a Task Force of the American Association of Oral and Maxillofacial Surgeons[3, 7]:
    - Current or previous treatment with a bisphosphonate;

- Exposed bone in the maxillofacial region persisting > 8 weeks; and
- No history of radiation treatment to the jaws.

- "ONJ-like" findings[2, 7]:
  - Current or previous treatment with a bisphosphonate;
  - Findings concerning for bisphosphonate-related ONJ but not meeting the case definition; exposed bone < 8 weeks duration; such as purulent osteomyelitis.
- Stage 0 BRONJ (based on radiographic evidence)[6, 4] in PROBE examined respondents who reported dental symptoms, referred to in this summary as stage 0 disease[6]:
  - Current or previous treatment with a bisphosphonate; and
  - No clinical evidence of exposed or necrotic bone;
  - Concerning radiographic findings including dense sclerotic bone, thickening of the lamina dura, persistence of unremodeled bone in extraction sockets

The primary risk factor, or predictor of interest, based on published literature, was OBP treatment duration*. The other risk factors were assessed for their association with OBP duration of < 2 year, 2-3.9 years, and ≥ 4 years instead of their association with ONJ because the relatively small number of identified ONJ cases limits the interpretation of statistical analyses. Standard descriptive statistical methods, ANOVA and chi-squared tests, and secondarily ordinal logistic regression were used. If the variable was associated with OBP duration ($p<0.2$), was reported in the cases, and was associated with ONJ in a logistic model of only ONJ and that variable ($p<0.1$), then those variables were assessed for their association with ONJ in the final logistic regression model with OBP exposure as < or ≥4 years. The OBP duration categories were chosen because there were no ONJ cases with OBP exposure of <2 years and the relation of ONJ to OBP duration was not linear[†] (5 cases occurred between 4.1 and 4.9 years, whereas the other 4 cases occurred at 2.6, 3.0, 5.6 and 6.0 years of OBP exposure). These analyses were repeated for the composite outcome of jaw complications that included ONJ, ONJ-like, and Stage 0 disease.

3 RESULTS OF STUDY

Out of the 13,946 patients who received prescriptions for an OBP for at least one year with at least one prescription in 2006 and who were mailed the survey, 8,572 (61.5%) responded. Of the 2,159 (25.2%) reporting dental symptoms, 1,005 received dental examinations and an additional 536 patients had their dental records reviewed.

3.1 RESULTS OF PHASE I – PREVALENCE OF ONJ IN OBP USERS

The study investigators identified nine cases of ONJ (meeting pre-defined outcome definition including at least 8 weeks of exposed bone), all classified as stages 1-2 (descriptions of ONJ stages[3, 4]). Stage 1 was characterized by exposed necrotic bone with no symptoms or infection, and stage 2 by exposed necrotic bone with pain and infection. Stage 3 includes evidence of stage 2 disease plus exposed necrotic bone extending beyond the alveolar bone region, pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border of the mandible (there were no cases of stage 3 ONJ identified in this study).

In addition, 10 cases meeting the pre-defined outcome definition for "ONJ-like" lesions were identified (three osteomyelitis, the rest with exposed bone, or osteolytic lesions). In 2009, after

[†] Note: This study does not attempt to identify an OBP duration below which there is no clinical risk due to the relatively small number of ONJ cases.

further delineation of the spectrum of dental signs leading to ONJ, including Stage 0 disease, the investigators identified an additional 10 cases of Stage 0 disease, with radiographic evidence only (yielding 29 total cases overall).

The prevalence of ONJ (n=9) among 8,572 survey responders was 0.1% (95% confidence interval 0.05% to 0.20%) or a frequency of 28 (95% CI 14 to 53) per 100,000 person-years of oral bisphosphonate treatment.

Most of the ONJ cases (7 of 9) had 4 or more years of OBP exposure for a prevalence of 0.21% compared with 0.04% for less than 4 years OBP exposure (1 case at 2.6 years and 1 at 3.0 years of OBP exposure). There were no cases of ONJ among patients with less than 2.6 years of OBP exposure.

The size of each visible ONJ lesions identified in this study ranged from 2-12 mm. Patients with ONJ at extraction sites tended to have larger ONJ lesions than those without extractions.

Additional clinical information described for each ONJ case included:

- Past History of ONJ cases:
    - Four had a history of dental extraction 8-17 months previously (one with a fistula to bone),
    - Five had no history of predisposing factors; however,
        - Three had a torus (boney protuberance inside mouth, all palatal).
- Oral bisphosphonate duration of therapy for ONJ cases:
    - One at 2.6 years,
    - One at 3.0 years, and
    - Seven at ≥4 years.
- One Year Follow-Up of the nine ONJ cases:
    - Most patients (five) had not healed after one year (all four dental extractions had not healed: two mandibular lesions required surgical debridement one of which had a predisposing fistula to bone and was worsening, two were maxillary lesions; and the last non-extraction patient had no predisposing factors)
    - One lesion was nearly healed (history of palatal torus), and
    - Three healed (two palatal tori healed after exfoliation of exposed bone, and a third had no predisposing factors).

3.2 RESULTS OF PHASE II – EVALUATION OF RISK FACTORS

The demographic risk factors were descriptively presented for the 8572 survey respondents in tabular form in the analysis section of the Final Report. They included the following characteristics: 93% female, 77% aged 60-69 years, 71% white, 18% Asian, 22% denture use, 6.6% tooth extractions.

The risk factors and their association with the duration of OBP were analyzed statistically and nine variables with a $p<0.2$ were analyzed in separate logistic regressions for an association with ONJ and jaw complications ($p<0.10$) leading to final models with only 4 and 3 risk factors respectively. Thus, a p-value was used twice in selecting possible risk factors.

The variables found to be associated with OBP duration, categorized as < or ≥4 years, were age, female gender, race/ethnicity, body weight, diabetes mellitus, rheumatoid arthritis, current smoker, oral glucocorticoids (> 2gm prednisone equivalent in the prior year), and any estrogen use in the prior year. Since there was no overlap in distribution between ONJ cases and non-cases, five variables were dropped, four (age, body weight, rheumatoid arthritis, and

glucocorticoid use) were tested in logistic regression models for an association with ONJ ($p<0.1$). Age and rheumatoid arthritis met the p-value threshold ($p<0.1$) and were included in the final model.

OBP duration ≥4 years had an increased odds ratio of 4.45 for ONJ after adjustment for age and rheumatoid arthritis but the statistical significance was borderline at $p=0.06$.

In similar analytic steps, OBP duration ≥4 years had an increased odds ratio of 2.11 for the composite outcome of ONJ, ONJ-like, and Stage 0 disease, after adjusting for age, smoking and glucocorticoid use in the final model, that was statistically significant, $p=0.05$.

In summary, in an OBP-exposed cohort, the risk factors that showed a trend toward association with ONJ were OBP duration greater than 4 years, older age (which may reflect poorer oral health), and rheumatoid arthritis (which may reflect increased glucocorticoid use and immunomodulatory agents).

3.3 RESULTS – PUBLICATIONS AND WRITTEN DOCUMENTS

There are three publications based on the OBP-exposed survey respondents in this study:

1. Prevalence of ONJ in OBP-exposed patients (0.10% (95% confidence interval 0.05% to 0.20%)[2]
2. Implant failures in elderly OBP-exposed women (16 implant failures in 589 reporting dental implants) [5]
3. Radiographic findings in Stage 0 disease in OBP-exposed patients (10 Stage 0 disease cases in 30 patients with dental symptoms without exposed bone who had radiographic evaluations)[6]

Another manuscript submitted for publication covers the dental health of OBP-exposed patients.

The investigators' final report on this study[7], submitted to FDA in early September 2010, includes an overview of phase I, determining the prevalence of ONJ in OBP-exposed patients, and a review of phase II, an evaluation of the possible risk factors.

4 COMMENTS & DISCUSSION

The PROBE study provides an estimate of the prevalence and describes the spectrum of severity of ONJ among a defined population of mostly women exposed to OBP. It also generates hypotheses about several important risk factors for ONJ.

The prevalence of ONJ among the OBP-exposed responders (9 cases/8,572 respondents[‡]) was 0.1% (95% confidence interval 0.05% to 0.20%). The frequency was 28 (95% CI 14 to 53) per 100,000 person-years of oral bisphosphonate exposure. This is higher than the estimated 0.001-0.01% ONJ prevalence in OBP-exposed populations and lower than the estimated 1-5% ONJ prevalence in IV BP-exposed populations. This is likely due in large part to this study's direct patient survey and oral examinations compared to cohort studies in electronic medical databases or medical records, especially those done before ONJ was assigned its own ICD-9 code in 2007.

This PROBE study also describes a spectrum of oral and dental morbidity especially the radiographic changes possibly along a spectrum of ONJ development which were eventually described by the American Association of Oral and Maxillofacial Surgeons in 2009[4]. The clinical

[‡] Note: The 8,572 respondents are a subset of the 13,946 patients identified with at least one year of chronic bisphosphonate prescriptions who were mailed the survey.

findings identified in this study are consistent with the observation that cases of OBP-associated ONJ are generally less severe than those associated with intravenous IV bisphosphonates. Nonetheless, five of the nine ONJ cases identified in the PROBE study had not healed after one year of follow-up. Two of these were mandibular ONJ lesions, one of which had an oral fistula, and both required surgical debridement. This suggests that the clinical spectrum of OBP-associated ONJ can include serious and recalcitrant cases as well.

The PROBE study lends support to the hypothesis that a longer duration of OBP treatment may increase the risk of ONJ. This study was undertaken just as the knowledge of ONJ associated with OBPs was becoming widespread and prior to AAOMS recommending discontinuation of IV BPs and OBPs taken longer than three years before dentoalveolar surgery until after adequate healing[3]. Therefore, it provides a unique look directly at the patients receiving chronic OBPs and at those with oral symptoms before well-defined guidelines were instituted by most healthcare practitioners.

4.1 STRENGTHS OF THE STUDY

The unique strength of this PROBE study is that the information was obtained from direct patient surveys and, for those with dental or oral symptoms (potential ONJ cases), from follow-up dental examinations and healthcare records review. Another strength is the timeliness of the data collection. This study was conducted after published reports suggested an association between ONJ and IV BPs but before a potential shift in the prescribing practices of OBPs for osteoporosis before and after dentoalveolar surgery[3] and before the introduction of Reclast® (IV zoledronic acid) in 2007 as treatment or prevention of osteoporosis. The third strength is that this was a population-based study which identified all OBP-exposed patients for the survey who lived in a defined geographic area and were covered by a large health care system which included more than one third of the insured and diverse population in the San Francisco area.

4.2 LIMITATIONS OF THE STUDY

The main limitation of this study is that, due to the anticipated rarity of ONJ in the study population, surveying a large, unexposed comparison or control group was deemed prohibitive by the investigators, therefore relative risk for the association between OBP exposure and ONJ could not be estimated.

Other limitations included

1. The OBP exposure was mostly alendronate/Fosamax (99.2% (8503/8572) of survey respondents; 99.0% (2137/2159) of patients who reported dental symptoms; all ONJ and ONJ-like cases (n=19) were exposed to alendronate with one also exposed to risedronate). This pattern is consistent with overall drug utilization patterns for OBPs in the US in that alendronate is the most prescribed OBP (~60%) in the US. It is not clear if these results can be generalized to other users of OBPs.
2. The low survey response rate (61.4%, although this is good compared to most surveys) which could bias interpretation of the representativeness of the findings,
3. Restriction of the population to insured families and to the San Francisco geographic area,
4. Non-responders were not included in the analyses, and
5. Underrepresentation of the elderly Medicare population.

Finally, this study provided the data for a prevalence of ONJ in a defined population of OBP users; however, due to the methodological limitations mentioned earlier and the relatively small

numbers of adjudicated ONJ cases (9 ONJ cases out of 8,572 respondents), it is difficult to support statistical inference for risk factors. Therefore, as described in section 4.3, it is best to view the findings of this study as descriptive and not rely on statistical calculations for interpretation of the clinical findings.

4.3 COMMENTS ON STATISTICAL ANALYSES FOR RISK FACTORS

As mentioned above, statistical inference is limited; however, descriptive information is valuable, and is based on well documented clinical evaluations, a unique feature of this study. Interpretation of p-values and other statistical inferential statements as noted in the Final Report should be carefully considered since they could be the result of poor behavior of the statistical methodology and not necessarily the result of clinically meaningful evidence. Because of the limited evidence provided by the relatively small number of ONJ cases, it is difficult to support conclusions based on statistical inference alone. The descriptive portion of the assessment is much more informative and is more appropriate and consistent with the primary goals of these cross-sectional studies.

5 REGULATORY CONSIDERATIONS

Fosamax (alendronate), the first oral bisphosphonate indicated for osteoporosis treatment or prevention, was approved September 29, 1995. Actonel (risedronate) and Boniva (ibandronate) followed in 1998 and 2003. Initial regulatory action regarding the OBPs and ONJ was in the form of class labeling to include ONJ as an adverse event in the IV BP's and OBP's labeling. By the end of 2005, all three OBPs had ONJ listed as an adverse event in their labeling.

5.1 REGULATORY RECOMMENDATIONS

The Kaiser researchers have communicated the results of the OBP ONJ (PROBE) study in at least three publications in the Journal of Oral and Maxillofacial Surgery. Since ONJ is already labeled to some extent for the OBPs, it is important for FDA to communicate the key findings and clinically relevant information regarding the results of this study to potential OBP prescribers and patients. These findings include:

- Nine cases of ONJ were identified among 8572 survey respondents in the PROBE study, representing a prevalence of 0.01% (95% confidence interval 0.05% to 0.20%). However, out of the 13, 946 patients identified as receiving at least one year of OBP prescriptions, the ONJ status of the non-responders is not known.
- Information on predisposing factors for nine adjudicated ONJ cases identified in the PROBE study:
    - Four (44%) ONJ lesions were located at dental extraction sites;
    - Three (33%) ONJ lesions were located on a maxillary palatal torus;
    - Two (22%) ONJ cases had no identified predisposing factors other than OBP exposure.
- The size of exposed bone for the nine ONJ cases ranged from 2 x 2 mm to 12 mm or 4-113 mm^2 with a mean of 29.7 mm^2 and a median of 24 mm^2.
- The symptoms reported were mostly painless (3 patients) or focal pain (4 patients, one with erythema), but two had purulence (one with swelling, the other with a fistula to bone, pain, swelling, and paresthesia).
- The PROBE ONJ lesions (>8 weeks of exposed bone) were stages 1 and 2. There were no stage 3 ONJ cases.

- Stage 1 is exposed necrotic bone without symptoms or infection (n=2)
- Stage 2 is exposed necrotic bone with pain and infection (n=7)
- Stage 3 is exposed necrotic bone extending beyond the alveolar bone region with pain and infection

- The degree of healing of nine adjudicated ONJ cases after one year of follow-up:
  - Five (56%) lesions had not healed (including all four cases with prior dental extractions, of which one with a fistula to the mandible was worsening, and required surgical debridement);
  - One lesion was "nearly healed" (history of palatal torus);
  - Three (33%) lesions had healed (two cases with a palatal torus resolved after exfoliation of exposed bone).
- Ten "ONJ-like" cases were identified among the 8,572 PROBE survey respondents
  - ONJ-like cases were defined as having: 1) Current or previous treatment with an OBP; and 2) Findings concerning for BRONJ but not meeting the case definition; exposed bone < 8 weeks duration; such as purulent osteomyelitis
- Ten Stage O cases were identified among the 8,572 PROBE survey respondents
  - Stage O BRONJ (based on radiographic evidence) were defined as having: 1) Current or previous treatment with an OBP; 2) No clinical evidence of exposed or necrotic bone; and 3) Concerning radiographic findings including dense sclerotic bone, thickening of the lamina dura, persistence of unremodeled bone in extraction sockets
- Findings of the PROBE study are consistent with an increasing risk of occurrence of ONJ with an increasing duration of OBP exposure (1 ONJ case at 2.6 years OBP exposure, 1 case at 3.0 years exposure, and 7 out of 9 ONJ cases had ≥4 years of OBP exposure, prevalence of 0.21%).
- The OBP exposure context is that in 2007 there were 5.4 million people in the US exposed to OBPs, about 5.7 million people in 2008, and about 5.2 million in 2009 (based on retail pharmacy data, and not counting mail order sources of OBPs).
- Given the widespread use of OBPs, often in patients who have no pre-existing clinical disease (i.e. primary prevention of osteoporosis), the balance of benefit and risk should be carefully considered in light of the well-documented risk of potentially recalcitrant ONJ lesions in patients receiving chronic OBP therapy, and especially in patients requiring dental extractions or dental implants.

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Appendix 5: Moeny 2011 FDA Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	7-5-2011
Through:	Judy Staffa, Ph.D, R.Ph. Acting Director Division of Epidemiology (DEPI) Office of Surveillance and Epidemiology (OSE) Rita Ouellet-Hellstrom, PhD, MPH Epidemiologist Team Leader, DEPI/OSE Laura Governale, Pharm.D., MBA Drug Use Data Analyst Team Leader, DEPI/OSE
From:	CDR David Moeny, MPH, R.Ph., USPHS Epidemiologist, DEPI, OSE Patty Greene, Pharm.D. Drug Use Data Analyst, DEPI/OSE
Subject:	Literature review of atypical femoral fractures and their association with bisphosphonate use
Drug Name(s):	Fosamax (alendronate sodium), Actonel (risedronate sodium), Boniva (ibandronate sodium), and Reclast (zoledronic acid)
Applicant/sponsor:	Merck (alendronate), Novartis (zoledronic acid), Roche (Ibandronate), Warner Chilcott (risedronate)
OSE RCM #:	2010-588

CONTENTS

EXECUTIVE SUMMARY

The bisphosphonates are a drug class which is widely used to treat and prevent osteoporotic related bone fractures. This class of drugs has been proven effective at reducing the incidence of hip fracture (3, 5, 16), a significant cause of mortality among the elderly. A number of case reports and case series published since 2005 have raised the question of a potential safety signal of "atypical" femoral fractures associated with bisphosphonate use. These atypical fractures are characterized by their association with no or minimal trauma, cortical thickening of the bone, and "beaking" at the fracture point. Media reports around the issue have raised the level of concern among the public, presumably increasing the risk that patients may stop treatment thus placing themselves at a greater risk of disabling fractures.

This review provides background around the issue of femoral fractures in general, and atypical fractures in particular, and summarizes the epidemiological literature addressing this potential safety signal. The focus of the literature review is on case control, cohort studies, and randomized controlled clinical trials.

Three principal clinical trials of bisphosphonate efficacy (the 3 year HORIZON, 5 year FIT and 10 year FLEX) included fractures as endpoints; initially these studies combined femoral fractures into the "other fractures" category making the distinction with atypicality difficult at best. The studies found that bisphosphonates prevented "other" fractures. However, low energy fractures were not a measured outcome.

The clinical trials did not specfically use femoral fratures as endpoints. A secondary analysis of the clinical trial data conducted to examine femoral fractures found that compared to controls, bisphosphonate users were no more likely to experience a femoral fracture The secondary analysis was not able to use radiographs for the overwhelming majority of case classification, however, which casts doubt on the findings because of the importance of radiography in accurately defining atypical fractures.

The observational studies have shown that low energy femoral fractures occur in both treated and in untreated patients. Bisphosphonate users appear to have time related changes in bone morphology (increased cortical thickening), but the significance of this finding in terms of increased risk of fracture is unknown. The case control, cross-sectional, and cohort studies conducted to date suggest that bisphosphonate users may have an increased risk of low energy subtrochanteric femoral fractures, and that the risk may be increased by long term exposure to bisphosphonates. However, these studies have been hampered by reliance on administrative claims data without access to x-rays for case classification.

A study using a data resource which contains a long history of bisphosphonate use, access to original radiographs, full medication history, and a large number of study subjects is needed to definitively assess the atypical fracture safety signal.

1 BACKGROUND

1.1 INTRODUCTION

The bisphosphonates are a drug class widely used to treat and prevent osteoporotic related bone fractures. This class of drugs has been proven effective at reducing the incidence of hip fracture, a significant cause of mortality among the elderly. A number of case series, however, have been published over the last 6 years describing unusual femoral fractures which were identified in patients taking bisphosphonate drug products (2, 4-9, 15, 16).

In response, several epidemiologic studies were conducted which attempted to determine whether bisphosphonates were associated with an increased risk of these "atypical" fractures.

Meanwhile, recent media attention has spurred concern among the general public. While it is generally recognized among health care practitioners that the benefits of bisphosphonate therapy outweigh the risk of atypical fractures (1, 12) , the actual risk of atypical fracture associated with bisphosphonate use is unknown, leading some patients to discontinue therapy, or to decline therapy altogether.

Given the public health issues surrounding hip fractures and the resultant morbidity and mortality, it is critical to assess the risk of bisphosphonate therapy and to guide both the medical community and patients in the selection of appropriate osteoporosis therapy.

This review is undertaken to inform OSE and OND on the current state of research into this safety question, to provide background for the decision making process, and to guide the development of additional observational epidemiology studies.

Osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and increased risk of fracture. It is estimated that the lifetime risk of an osteoporotic fracture is 40-50% in women and 13-22% in men. The morbidity of hip fracture is high: only approximately 50% of fracture patients regain pre-fracture levels of mobility (14) and up to 20-30% of hip fracture patients die within 1 year of the hip fracture date.

Bisphosphonates and the prevention of fracture

Bisphosphonate treatment has been shown to reduce the risk of hip fractures by approximately 50% (3, 5, 16). Given the high rates of osteoporosis and the benefits of bisphosphonate therapy, the utilization of these products is correspondingly high. Based on U.S. outpatient retail pharmacy data, 1 in 10 women over age of 55 years of age received a prescription for a bisphosphonate drug during 2009 alone. The proportion of men receiving a bisphosphonate during the same year was 1 in 100[1].

[1] Patient estimate obtained from SDI Health, Total Patient Tracker, extracted 3/2010, U.S. population estimate U.S. census estimate for 6/2009.

Bisphosphonates and Atypical Fractures

Initially, from case series, a definition of atypical fractures has evolved to include the location of the fracture, as well as specific features of the bone and fracture seen in the radiological images. Figure 1 presents the location terminology used in the diagnosis of femoral fracture, along with the ICD-9 codes for the fracture location.

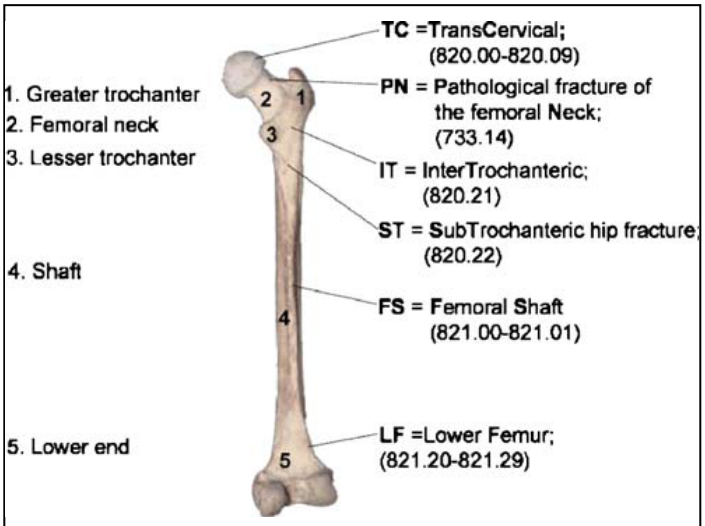


Figure 1. Femoral fracture locations with ICD-9 codes (Nieves et al)

A number of case or case series reports have been published which suggest that a particular fracture pattern (deemed "atypical") may be associated with the long-term use of bisphosphonate products in both men and women (2, 4-9, 15, 16). These publications primarily focused on evaluation of subtrochanteric and/or proximal diaphyseal femur fractures that occurred in patients using bisphosphonates and attempted to describe the specific radiological patterns seen. This particular fracture / radiographic pattern presented in these cases (low energy, cortical thickening, "beaking", transverse), is representative of low energy femoral fractures in general and these atypical fractures are thought to be uncommon(13).

1.2 PRODUCT LABELING

Bisphosphonates and the prevention of fracture

The first bisphosphonate approved for the treatment of postmenopausal osteoporosis was Fosamax (alendronate sodium) in 1995. Actonel (risedronate sodium), Boniva (ibandronate sodium), and Reclast (zoledronic acid) were approved in 2000, 2003, and 2006 respectively.

Information on approved bisphosphonate products is summarized in Appendix 1 Table 1.

Most of these drugs are now available in multiple dosing regimens for osteoporosis treatment and prevention. The dosing for these products ranges from daily to monthly for oral preparations and every three months to once yearly for intravenous preparations. The complete listing of bisphosphonate products is presented in Appendix Table 1.

1.3 INDICATIONS FOR USE

Bisphosphonates are indicated for

1. Postmenopausal osteoporosis, there are currently two approved indications:
    a. Treatment of osteoporosis in postmenopausal women (or women at high risk of fracture,)
    b. Prevention of osteoporosis in postmenopausal women

2. Treatment to increase bone mass in men with osteoporosis
3. Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids
4. Treatment of Paget's disease of bone in men and women

2 METHODS AND MATERIALS

This document includes a review of the literature and an assessment of the manner and frequency of current bisphosphonate use in the U.S. for the prevention and treatment of osteoporosis.

2.1 DATA AND INFORMATION SOURCES

To inform the FDA's understanding of atypical fracture and to guide in the further review of this regulatory issue, a PubMed search was conducted utilizing the following search terms: ((((("Alendronate"[Majr] OR "pamidronate "[Substance Name]) OR "ibandronic acid "[Substance Name]) OR "risedronic acid "[Substance Name])) AND "Femoral Fractures"[Majr]. The search was limited to studies in humans and publications in the English language only. Articles retrieved were examined for content and selected for review if they were cohort, cross sectional, case-control, or randomized clinical trial (RCT_ studies. The time period searched was from the introduction of alendronate (the first bisphosphonate approved for osteoporotic indications) in 1995 to April 2010. All literature cited by the final reviewed articles was also checked to determine if it was appropriate for inclusion in this review.

A total of 68 articles were identified for possible review; 58 were excluded for review because they were case reports, case series, letters to the editor, review articles, or did not address atypical fracture. The search yielded 9 articles for review; 6 observational studies and 3 RCTs that qualified for review based on our selection criteria.

2.2 DRUG UTILIZATION DATA SOURCES

The IMS Health, IMS National Sales Perspectives™ (see Appendix 3 for full description) was used to determine product distribution by setting of care for alendronate, risedronate, ibandronate, and zoledronic acid. In this review, we examined nationally projected estimates of use in the outpatient retail pharmacy setting and non-national patterns of use in a sample of clinic settings, excluding mail order pharmacy.

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

Outpatient use and patient demographics (stratified by ages 0-40, 41-49, and 18+ years) were identified from SDI, Vector One®: National (VONA) and Total Patient Tracker (TPT) (***Appendix 3***). From these data sources, estimates of the number of dispensed prescriptions and patients who received a prescription for alendronate, risedronate, or ibandronate were obtained from years 2002 through 2009, inclusive.

Using the database Wolters Kluwer Source Lx®, we obtained the number of unique patients receiving zoledronic acid in an unprojected US sample of patients from years 2008 and 2009. Patients who submitted a prescription claim for zoledronic acid were searched using the national drug code (NDC code: 0078-0435-61). Medical claims were captured using the procedure code for zoledronic acid administration (J-code: J3488).

3 RESULTS

Studies reviewed are summarized in Appendix 1 Table 2.

3.1 OBSERVATIONAL STUDIES

3.1.1 Salminen, et al.

In a cross sectional study, Salminen et al (13) identified all femoral fractures among hospitalized patients 15 years of age and older in a Finnish semi-urban county during a 10 year period from 1985 through 1994. Fracture cases were identified using a computerized search of medical records then the complete medical record (including radiology film) for each patient was reviewed to classify the fracture type. Fractures were classified as high vs. low energy. Low energy fractures were defined as having occurred due to a "fall from a height of 1 meter or less, slipping or stumbling at ground level, crush and sports injuries." The location and fracture type (oblique, spiral, transverse) were recorded. Pathologic fractures (due to metastases, etc) were excluded.

The incident femoral fracture rate in this population was 12.1 per 100,000 person-years. Of the 201 fractures identified, 50 (25%) in 37 patients were classified as low energy fractures. Low energy fractures were primarily seen in older patients and tended to be spiral in nature.

This study is significant in that it provides a prevalence rate for low energy fractures from the period before the widespread introduction of bisphosphonate use. The study is limited by its failure to assess medication use as a possible risk of fracture, the inability to assess the osteoporotic status of fracture cases, and the assumption that all fractures identified were incident (new) fractures. The study's estimate of fracture incidence assumes that all patients with a fracture within the studied county received treatment at one of the two catchment hospitals, and that all residents of the county were at the same risk of low energy fractures. The uncertainty of these two assumptions likely caused the result to be an underestimation of the actual fracture rate.

3.1.2 Nevasier et al

Nevasier et al(11) (2008) conducted a retrospective review of femoral fractures among patients admitted to a New York trauma center between January 2002 and March 2007. In contrast to the previous study, the investigators attempted to specifically characterize low energy fractures and to examine the duration of bisphosphonate use among fracture cases. Potential cases of subtrochanteric or femoral fractures for this study were identified using ICD-9 codes 820.2 through 821.0. Patients were excluded from the study if the fracture was high energy (car accident, trauma, etc) and if the fracture was at or below the distal third of the femoral shaft or was pertrochanteric. The radiographs were reviewed by orthopedic surgeons who were blinded to patient exposure status to identify fractures with a pattern consisting of a "simple, transverse, or short oblique pattern in areas of thickened cortices with a unicortical beak", i.e. an atypical fracture.

The investigators identified 70 femoral fractures for review. Of these, 25 (36%) had documented bisphosphonate use. Alendronate was the only bisphosphonate used for the fracture cases identified. Among these alendronate users, 19 of the 25 (95%) had an atypical fracture pattern; the atypical fracture pattern was seen in 1 of the patients with no bisphosphonate use. The investigators were able to determine duration of alendronate

therapy in 16 of 19 patients. Among alendronate users with the atypical fracture pattern, the average duration of alendronate use was longer at 6.9 years compared to 2.5 years in users without the atypical pattern. This difference was statistically significant (P = 0.002). Among the 45 fracture patients who did not exhibit the simple-transverse-thickened cortices pattern, only one was an alendronate user. The authors determined that alendronate use was a significant risk factor for the atypical fracture pattern (OR 139.33, 95% CI [19.0-939.4]).

The authors demonstrated that, in this analysis, atypical fractures were strongly associated with bisphosphonate use and that the duration of bisphosphonate use was associated with developing the morphology which has come to be recognized as characteristic of the radiograph of an atypical fracture.

The study's strengths included the access to trauma center records and the blinded review of the original radiograph. This study was limited by the inability to obtain information on the duration of bisphosphonate use for all case patients (only contacted 26% of the 70 cases) and by the small number of cases reviewed. If the cases reviewed were not representative of all cases, then it is possible that information bias was introduced which could bias the risk estimate toward or away from the null. There is also a possibility of misclassification bias as 16% of alendronate patients had no treatment indication recorded.

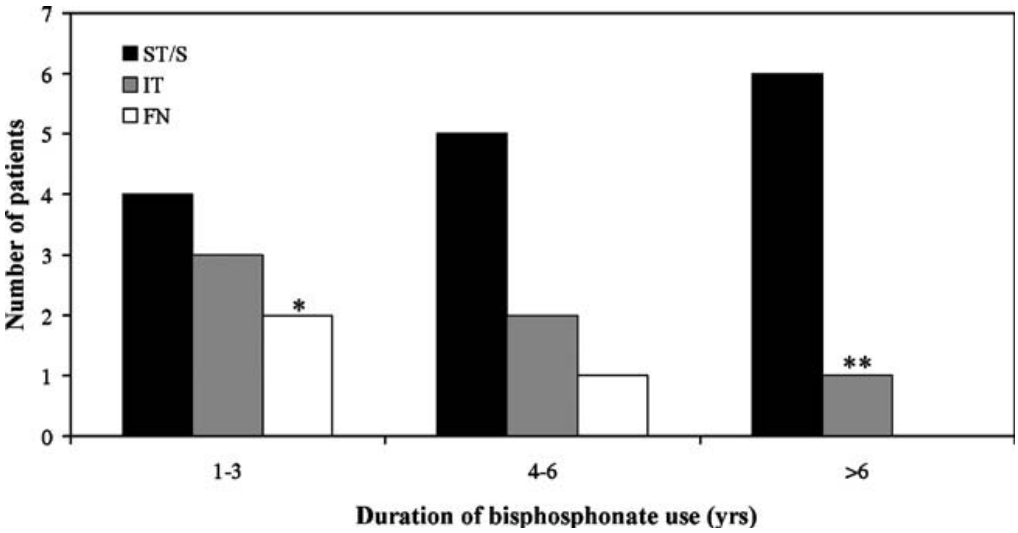
3.1.3 Lenart et al

In a retrospective case control study with the goal of determining if duration of bisphosphonate use was associated with the atypical fracture risk, Lenart, et al(10) examined duration of bisphosphonate use in a subset of cases originally identified in the Nevasier 2008 study, and extended case identification back to 2000 instead of 2002. Although Neviaser included men and postmenopausal women with fracture codes 820.2 (intertrochanteric, subtrochanteric and femoral shaft) Lenart further restricted the case selection by including only subtrochanteric or femoral shaft fractures in postmenopausal women and excluding those with diseases and drug products known to increase fracture risk. The investigators matched the 41 subtrochanteric or femoral fracture cases to 82 low energy intertrochanteric (n=41) and femoral neck fracture (n=41) controls on the basis of age, race and body mass index. Fractures were confirmed via radiology. Patients were excluded if they had pre-existing bone metastases, osteogenesis imperfecta fibrous dysplasia, renal impairment, hyperthyroidism or hyperparathyroidism, active malignancy, osteomalacia, vitamin D deficiency, history of peptic ulcer or esophageal disease in the previous year. The x-ray "atypical" pattern of interest was defined as "a simple subtrochanteric/shaft fracture with cortical thickening and beaking of the cortex."

Bisphosphonate use occurred in 15 of 41 (37%) cases compared to 9 of 82 (11%) controls (OR 4.4 95% CI 1.8-11.4). The identified x-ray pattern of "a simple transverse or oblique fracture with beaking of the cortex on one side and cortical thickening around the site of fracture", was significantly associated with bisphosphonate use (OR 15.33, 95% CI 3.06-76.90). The pattern of cortical thickening itself was significantly associated with the duration of bisphosphonate use in subtrochanteric/shaft cases taking a bisphosphonate (Spearman's rank correlation, ρ, 0.7, P<0.001, Fig. 2). Additionally, the authors found that patients with subtrochanteric fractures were more likely to be on bisphosphonate therapy compared to the intertrochanteric/femoral neck fracture control group. For all patients on a bisphosphonate in the study, one femoral neck control patient was on risedronate and an intertrochanteric control was on etidronate then switched to alendronate. All other bisphosphonate users including all subtrochanteric users were taking alendronate. Patients

in the subtrochanteric group were on therapy for a statistically significant greater duration than those in the intertrochanteric group (p=0.01) or the femoral neck group (p=0.001). Cases of subtrochanteric fracture with the simple/thick cortices pattern were on bisphosphonate therapy a mean of 7.3 years (n=10) while those without the pattern were on therapy for a mean of 1.5 years (n=5).

Figure 2. Distribution of all fractures associated with duration of bisphosphonate use(10)



Fracture location: Black bars represent subtrochanteric/shaft (ST/S) fractures, grey bars represent intertrochanteric (IT) fractures, and white bars represent femoral neck (FN) fractures. Single asterisk: One patient in this group was taking risedronate. Double asterisks: This patient was taking etidronate for 5 years and then took alendronate for 2 years. (10)

This study showed that duration of therapy is an important factor in the occurrence of subtrochanteric femoral fracture and that there may be a differential risk for subtrochanteric versus interotrochanteric/femoral neck fractures. One advantage of this study is that there was enough power to allow for comparisons between cases and controls by fracture type. However, the case control study design is subject to several important biases, including selection and information biases. The investigators were unable to adequately assess historical indicators of osteoporosis history such as previous fractures, bone density scores, thyroid status and vitamin D levels; factors that would likely lead providers to place patients on bisphosphonate therapy. They were also unable to differentiate the effects of different bisphosphonates, since predominantly alendronate was used.

3.1.4 Abrahamsen et al

The publication by Abrahamsen et al (1) in 2009 consisted of a cross sectional analysis and a cohort study. The cross sectional analysis was designed to compare the atypical fracture rates by age, exposures and trauma mechanisms. The cohort analysis of patients with previous, hospital-treated non-hip or femoral fractures to determine whether any increase in subsequent atypical femoral fractures exceeded the increase in typical hip fractures (i.e. whether the benefit from use of bisphosphonates outweighed the risks of femoral fracture).

The cross sectional study used records retrieved from the Dutch medical records system to compare patient age, fracture mechanism, and exposures among patients with a

subtrochanteric or diaphyseal fracture (most frequently associated with atypical factures) during 2005. Medical claim records of hospitalized patients, age 60 years or older with a fracture of the proximal femur or hip were examined for recent use of alendronate or glucocorticoids, trauma mechanism (high vs. low energy) and patient age. The authors calculated the fracture rate per 1000 person years for subtrochanteric fractures, diaphyseal femur fractures and hip fractures. A total of 11,944 fractures were identified; 898 subtrochanteric femur, 720 diaphyseal femur, and 10,326 hip.

Alendronate use, trauma mechanism, and age were similar between hip fractures and subtrochanteric and diaphyseal femur fractures. Glucocorticoid use was more common among subtrochanteric fracture patients in whom 10.9% were alendronate users versus 6.7% of hip fracture patients.

The cohort study included 160,565 incident, non-hip fracture patients who were discharged from a hospital in Denmark between 1/1/1997 and 12/31/2005. Patients who stayed on alendronate therapy for 6 months or more after the index fracture date were enrolled in the treatment cohort (N=5,187) and assigned two randomly selected bisphosphonate unexposed controls. The controls were matched to cases on age, sex, fracture location (spine, shoulder, forearm, or other), and fracture date. The study endpoint was recurring fractures occurring >6 months after starting therapy. The fractures were identified using ICD-10 billing codes only since, for legal reasons, the identity of the patients was unavailable for linkage with x-rays and patient notes. Subtrochanteric second fractures occurred in 76 patients. After adjustment for baseline co-morbidity (number of co-medications, glucocorticoid use and Charlston index), alendronate use was associated with an increased Hazard Ratio for subtrochanteric / diaphyseal fractures, as well as for hip fractures (HR 1.46 95% CI [0.91-2.35 and HR 1.45 95% CI [1.24-1.74) respectively). The distribution between typical and atypical as second fractures was similar between alendronate treated and untreated patients. There were 178 patients who were highly compliant with alendronate use for > 6 years after their first fracture. Compared to their non-alendronate matched controls, long term use was not associated with increased risks of atypical femur fractures (p=0.74) in this cohort of prior fractures.

The authors were unable to discriminate between low and high energy fractures in approximately 40% of cases. No radiological assessment of atypicality was possible. The cohort study's long term use sub-analysis was underpowered with only 5 atypical fractures available for analysis.

3.1.5 Nieves et al

To further characterize the medication history and medical risk factors which may contribute to femoral fracture in the U.S. and the overall trends, Nieves et al (12) conducted an incidence study of femur fractures using the U.S. National Hospital Discharge Survey (NHDS) and a case-control study using MarketScan, a U.S. administrative insurance claims database comprised of Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases.

In the NHDS analysis, the investigators calculated rates of fracture discharges by obtaining the number of discharges for closed femoral fractures, stratified by type (using ICD-9 codes) and the U.S. civilian population from Census data for each year 1996 through 2006 as the denominator. The rates were directly standardized to the 2000 U.S Census. Eligible patients were age 50 and older with a minimum of 1 year of enrollment history between

2002 and 2006. Fracture patients were identified using the 8 ICD-9 code groups detailed below.

For the MarketScan study, cases were identified as patients age 50 years and older with a femoral or hip fracture and no hip or femoral fracture history in the 12 months prior. Rates of fracture incidence were calculated as the number of fracture cases divided by the number of person years of follow-up during that year and directly standardized using the year 2000 U.S. Census. In addition, a case control analysis was conducted by matching the hip and femoral fracture cases to 5 randomly selected non-cases based on age and gender during the year of fracture. The investigators stratified the cases and non-cases using 12 medical conditions and 9 prescription drug categories and reported that these appeared to be more common in cases than in controls. Fractures were classified according to the same scheme as that used in the incidence analysis. No significance testing was done for this portion of the study.

Fracture code groups for Nieves et. al. incidence and case control analysis included the following:

1. transcervical (including 820.00, intracapsular section, unspecified; 820.01, epiphysis; 820.02, midcervical section; 820.03, base of neck; and 820.09, other),
2. pathological fracture of neck of femur (733.14),
3. intertrochanteric (820.21),
4. trochanteric, unspecified (820.20),
5. hip fracture, unspecified part of neck of femur (820.8),
6. subtrochanteric (820.22),
7. femoral shaft (including 821.00, unspecified part of femur; 821.01, shaft)
8. lower femur (including 821.20, lower end, unspecified; 821.21, condyle; 821.22, epiphysis, lower; 821.23, supracondylar; and 821.29, other).

In the NHDS incidence study, the authors report that over a 10 year span with bisphosphonate availability, hospitalized hip fracture rates declined significantly from 600 per 100,000 woman years to 400 per 100,000 woman-years ($p<0.0001$). Over the same time, the rates of subtrochanteric, femoral shaft and lower femur rates remained relatively stable at approximately 20 per 100,000 woman years. The trends for men were similar, with lower incidence rates. Repeating this analysis using the MarketScan data from 2002-2006 found no significant fracture trend differences.

The MarketScan case control study examined the frequency of conditions and medications which are thought to increase the risk of fractures (previous fractures, osteoporosis, rheumatoid arthritis, other musculoskeletal diseases, diabetes, chronic obstructive pulmonary disease, renal disease, Alzheimer's and other mental illness, cardiovascular disease, and use of glucocorticoids, antidepressants, and proton pump inhibitors. The authors report that these drugs and medical conditions appeared to be more common among fracture cases, compared to controls. However, no significance testing was performed.

These incidence studies provided reassurance that the use of bisphosphonates may have a favorable risk benefit ratio: Rates of hip fractures have declined over time, while femoral fracture rates have remained stable. However, this study is limited by the inability to examine medical records and radiographs in order to assess whether the fracture was actually atypical, and the inability to exclude prevalent cases from the NHDS component.

3.1.6 Observational Studies: Summary

The observational studies conducted to date present somewhat contradictory results and have substantial design limitations associated with them. Overall, they suggest that there may be an increased risk of atypical fractures for users of bisphosphonate products, but do not completely answer the question as to whether any use of bisphosphonates is associated with this apparently rare outcome, and whether there is an increasing risk with duration of use of bisphosphonates for this fracture type. It is also important to note that these studies have shown that the atypical fracture type is also seen in non-treated patients at an estimated rate of 12 per 100,000.

3.2 RANDOMIZED CLINICAL TRIALS (RCTS)

The RCTs evaluated mostly the efficacy of bisphosphonate for the prevention of vertebral fractures. Some evaluated the effect on hip fractures but none assessed the benefit on femoral fractures especially atypical fractures.

3.2.1 Fracture Intervention Trial

The Fracture Intervention Trial (FIT) is a randomized blinded placebo controlled clinical trial conducted over 5 years to examine if alendronate reduced the risk of clinical and vertebral fractures in women with low bone density. Women aged 50 – 81 years old with no prior vertebral fracture were enrolled and followed for an average of 4.2 years. Subjects were randomized to placebo (2,218) or alendronate (2,214) and given supplemental calcium plus vitamin D if their calcium intake was low. Outcomes measured were new fractures, new vertebral deformity, and bone mineral density (BMD). Fractures that occurred during the study were classified as vertebral, hip, wrist or other.

Alendronate reduced clinical fractures (those fractures reported by physicians) by 36% in women with baseline osteoporosis bone density levels (BMD <2.5 SDs below normal). Compared to controls, the relative hazard of an "other clinical fracture" was 0.79 (95% CI 0.65-0.96). Significant reductions in clinical fracture occurred when the T score at the femoral neck and spine was -2.5 or less and less than -2.0 at the hip.

This study demonstrated the effectiveness of alendronate in fracture reduction, the primary endpoint and established the t-score for which alendronate treatment is effective. However, the study did not assess the safety of alendronate with respect to atypical femoral fractures. Fractures of the femur were grouped into the "other" category. This study also could not address the issue of long duration of use since patients were only followed for 4.5 years.

3.2.2 FIT Long Term Extension

The FIT Long Term Extension (FLEX) trial was a placebo-controlled open-label extension to the FIT trial. Schwartz et al conducted a 5 year post hoc analysis of the efficacy of continuing alendronate past 4 years. The primary outcomes were new fractures (vertebral or other), and bone mineral density (BMD) readings. Women who were in the alendronate treatment group in FIT and who had completed at least 3 years of previous bisphosphonate therapy were enrolled in FLEX and randomized to either placebo (n=437, 40%) or to 5 years of continued alendronate treatment at 5mg/day (n-329, 30%) or 10mg/day (n=333, 30%). For ethical reasons, women whose BMD T-score at flex baseline was <-3.5 (i.e. severely

osteoporotic) and whose pre-FLEX BMD was worse than their FIT baseline were excluded. Of the 2,852 women in the FIT study, 36% agreed to participate in FLEX.

This study found that the effect of long term use of alendronate in the prevention of fractures was dependent on baseline BMD. Women without prevalent vertebral fractures and whose BMD T-score was lower than -2 who continued on treatment had significantly fewer non-vertebral fractures compared to placebo (RR 0.50, 95% CI 0.26-0.96). Women with a BMD score >-2 (RR 1.41; 95% CI 0.75-2.66) did not benefit from continued bisphosphonate use.

The primary limitation of this study in the evaluation of atypical fractures is that it did not examine femoral fractures specfically, but simply grouped fractures into a non-vertebral group. As the study only enrolled 662 patients in the treatment group, the study is likely insufficiently powered to detect differences in atypical femoral fractures rates with a possible background rate as low as 12 per 100,000. The study also included only subjects who had been previously exposed to alendronate; no comparison to alendronate non-treated subjects was possible since even the FLEX placebo group had prior bisphosphonate use in FIT. Given the expected long-term effect of bisphosphonate treatment, prior treatment may have an impact on a patient's current risk of fracture. Finally, patients at very high fracture risk (those with very low BMD and those who had a declining trend of BMD measurements) were excluded from the study; potentially removing the patients who were presumably in greatest need of bisphosphonate prevention treatment.

3.2.3 Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial was also a randomized, double blind, placebo controlled trial in postmenopausal osteoporotic women(3). Postmenopausal women age 65-89 years of age with severe osteoporosis or those with moderate osteoporosis with a previous vertebral fracture (either one moderate or two mild fractures) were eligible for inclusion. Patients with previous use of a bisphosphonate for 48 weeks or more within 2 years of recruitment, as well as those with use of anabolic steroids or growth hormone with 6 months of randomization, or any previous use of strontium, parathyroid hormone, or sodium fluoride were excluded. Women who used other osteoporosis medications (calcitonin, raloxifene, etc) at time of randomization were not excluded, but patients were stratified by concurrent use status. Patients were assigned to one of three groups, two doses of drug or placebo, and were followed for 3 years of therapy, with a 1 year follow-up period after the last dose. The primary endpoints were vertebral fracture, osteoporosis related nonvertebral fractures (i.e. fracture which would likely not have ocurred in a non-osteoporotic patient), and BMD levels. There were 3861 patients enrolled in the placebo group and 3785 patients enrolled in the zoledronic acid group.

Subjects who received zoledronic acid had a 0.75 relative risk (RR) of non-vertebral fracture (95% CI 0.64-0.87) compared to placebo, and a 0.67 RR of any clinical fracture (95% CI 0.58-0.77).

The HORIZON trial demonstrated the effectiveness of zoledronic acid over the 3 year study period. Atypical fracture risk was not an endpoint in this study; these fractures would have been grouped with the other fracture categories. This study would have been underpowered (possible background rate as low as 12 per 100,000) and conducted for too short a time (3 years maximum) to examine the risk of atypical fracture.

3.2.4 Black et al

Black et al conducted a secondary analysis of the femoral fractures that occurred in the FIT, FLEX and HORIZON trials to evaluate whether there is an association between bisphosphonate use and atypical femoral fractures. Fractures that occurred during the trials were evaluated via radiology notes to determine the location. Where the original radiograph was available, the authors examined the morphographic characteristics of the fracture (i.e. transverse / oblique versus spiral, cortical thickening, cortical beaking, medial spiking, and contralateral similarity); however, the authors report that radiographs were rarely available. When the radiograph was not available, the radiology report was used instead. The relative risk of atypical fracture was calculated for each trial.

Among all three trials, there were 12 subtrochanteric or diaphyseal femur fractures among the 14,000 patients enrolled, with 51,000 patient years of follow-up. There were 2 fractures in FIT, 6 in HORIZON, and 4 in FLEX. The relative risk of subtrochanteric or diaphyseal fractures in the bisphosphonate treatment group compared to the control groups was not statistically significant for all three trials.

This study is notable for the fact that the authors examined the risk of atypical fracture within each study, instead of combining events in the three studies prior to analysis. This preserved randomization and avoided many of the biases which are inherent in other observational designs. However, the original radiographic images were not generally available, and the outcomes were primarily based on previously existing radiology notes. While the original studies provided adequate controls on radiology interpretation (rater training and inter-rater reliability testing), the original outcomes of interest were mostly vertebral and not femoral fractures and the notes might not have been as detailed as required for this analysis. Certainly, the assessment of whether the fracture was "atypical" could not be conclusively determined using the methods in this study. The authors have shown fairly convincingly that the benefits of bisphosphonates used for the prevention of hip and vertebral fracture exceed the estimated risk of femoral fracture. Finally, although the FLEX trial extended observation over a longer duration, both the FIT and HORIZON trials were limited to less than 4 years of observation. Given the hypothesis that duration of bisphosphonate use longer than 5 years is needed to observe bisphosphonate-related atypical fractures, increasing the person-years of observation by increasing the number of patients observed over a short time period does not the provide same information as increasing the person-years of observation for each person in the study. Therefore, in this situation, combining the study subjects to increase the person-years of observation failed to achieve the purported objective. Additionally, these clinical trials were conducted on a select group of patients and the findings may not apply to the general population of bisphosphonate users.

3.3 DRUG UTILIZATION

With the exception of Salminen et al study, the studies in this review were conducted between 2000 and 2006. For most of the studies, alendronate was the bisphosphonate most frequently associated with atypical fractures. Whether this is coincidence based on the fact that this product was marketed in 1995 prior to the availability of the other bisphosphonate products including the availability of a generic, or whether there is a product-specific effect, remains unknown. In an effort to assess the possibility that patterns of use are a viable explanation, a US-based bisphosphonate drug use analysis was undertaken.

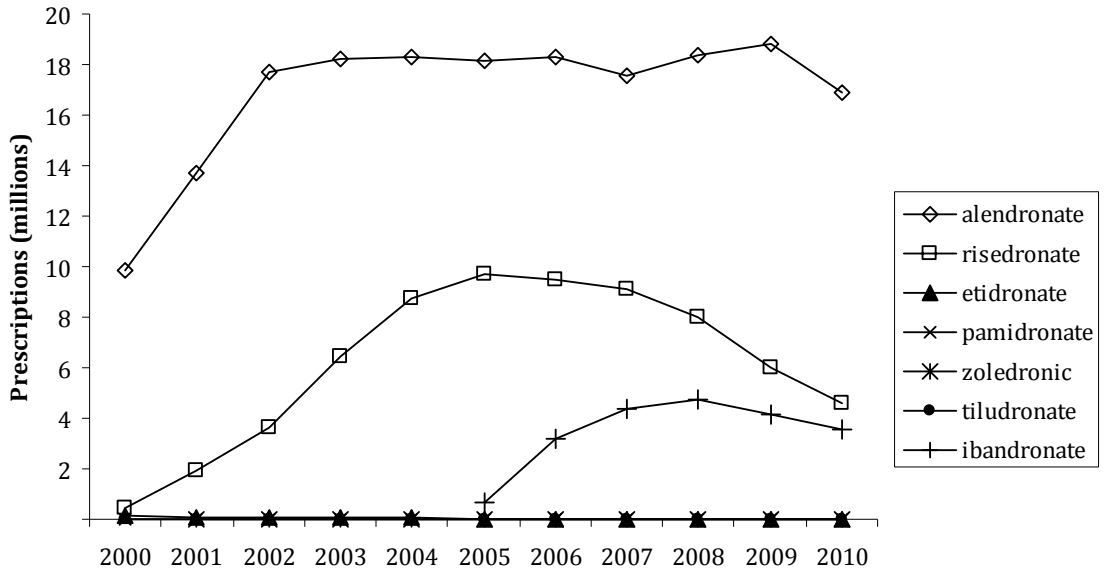
3.3.1 Wholesale Sales Distribution

With the exception of zoledronic acid products, the examination of wholesale data by bottles of tablets, individual packages, vials (Eaches) in year 2009 indicated that the majority of bisphosphonate use centered in the outpatient pharmacy settings (61-72% retail; 19-29% mail order, and 9-13% non-retail).[2] Outpatient pharmacy settings include chain, independent, and food stores with pharmacies. For the injectable product zoledronic acid, approximately 95% of the sales distribution was seen in the non-retail pharmacy settings, mainly clinics (non-retail 95%; mail order 3%, and retail 2%).

3.3.2 Outpatient Dispensed Prescriptions by Age and Sex

Figure 3 presents the nationally projected number of prescriptions dispensed from retail pharmacies for the bisphosphonate products from the year 2000 through the year to date ending November 2010. Alendronate was the first product available which was approved for osteoporosis and is available as a generic. As expected, alendronate dominates the bisphosphonate market. Alendronate products accounted for the majority of the total share with approximately 18 million prescriptions dispensed during each year since 2002 (Appendix 2, Table 2). For the years 2005 – 2009, alendronate accounted for 61% of all bisphosphonates dispensed through U.S. retail pharmacies (Appendix 2, Table 1). The outpatient retail dispensing of bisphosphonate is presented graphically in figure 3 below.

Figure 3. Nationally projected number of bisphosphonate prescriptions dispensed through U.S. retail pharmacies
Source: SDI, Vector One®: National



[2] IMS Health, IMS National Sales Perspectives™, Extracted 3/2010. Year 2009 File: 1003biph.dvr.

zoledronic acid was approved for and marketed for osteoporosis treatment in 2002. This product is administered in physician offices; therefore, its use is not completely captured in the retail pharmacy outpatient setting. In a sample of patients who submitted medical and prescriptions claims for intravenous zoledronic acid for years 2008-2009, demographic trends were similar to oral bisphosphonate trends for the same years observed. Patient claims increased by 150% from nearly 18,000 patients in year 2008 to 44,000 patients in year 2009.

3.3.3 Patient Demographics

We also examined the total projected number of patients receiving a prescription for alendronate, risedronate, and ibandronate products by age and sex from U.S. outpatient retail pharmacies for year 2005 through 2009 (Appendix 2: Table 3). The total number of patients prescribed these bisphosphonates increased by 2% from 5 million patients in year 2005 to 5.1 million patients in year 2009 for the selected products. Patients aged 60 years and older accounted for the largest proportion of prescriptions (71-78%). The majority of use was among female patients.

For zoledronic acid, patients aged 60 years and older accounted for the largest proportion of the patient prescriptions (85%) Similar to oral bisphosphonates, over 94% of claims were for female patients during this time period.

The dominance of the market by alendronate may provide an explanation as to why the literature for atypical fracture to date has focused on the risk associated with this product.

4 DISCUSSION

Our knowledge about the issue of whether bisphosphonates are associated with an elevated risk of "atypical" femoral fractures is currently evolving. This review presents a relevant summary of observational and intervention studies (cohort, cross-sectional, case-control, and RCT). While the RCT is generally considered the "gold standard" for assessing the efficacy of drug treatment, the trials available to date have not been designed to assess the risk of atypical subtrochanteric and femoral fracture as either a primary or secondary safety endpoint. The secondary analysis of the trial data by Black et al, attempted to address this limitation. However, Black did not have access to the source radiology films for the femoral fractures, instead relying on previously existing radiological notes. As noted above, atypical fracture risk is a recently evolving safety issue, and the original radiologists may not have noted fracture features that now appear to be important for an atypical fracture case definition. Furthermore, Black did not examine medication use (such as steroids) that might contribute to an increase in fracture risk, also an important co-variant(12).

Each of the observational studies has taken a slightly different approach to evaluating whether there is an excess risk with bisphosphonate use, but all are limited by a number of factors. The primary limitations to these studies are a lack of statistical power and, in most, the availability of radiographic images. Salminen et al provided an estimate of the incidence of low energy fractures in the period before the widespread use of bisphosphonate (~1/10,000 person years). While this may be an under-estimate of the true risk due to the potential for incomplete capture of cases, it provides an estimated baseline and context for the study by Nieves which found an increased risk of 2.5 per 10,000 person years with bisphosphonate use. Using these estimates, a cohort study would need a total cohort size of 250,000 patients to detect a relative risk of 2 with a 2 sided alpha level (type I error) of 0.05, beta level (type II error) of 0.02 (power of 80%), a case control ratio of 1:1, and a 75%

prevalence of bisphosphonate exposure. Using the same power, alpha and risk differences, a case control study would require roughly 140 cases in each group. The study population will also need to be rich in patients with longer available and documented histories to adequately examine the effect of duration of use since it is hypothesized that the risk of atypical fractures associated with bisphosphonate use occurs mostly in long-time users.

The observational studies to date have also been hampered by the inability to access the source medical records, especially the radiology images. Given the descriptive nature of the case definition of atypical femoral fractures, the ICD-9 coding system is only helpful in the initial broad selection of potential cases. Additionally, access to bone density measurements, medication history (including bisphosphonate type and duration of treatment), past fracture history, corticosteroid use, and, vitamin D status (if available) would be important to more fully characterize the fracture risks (if any) that are associated with bisphosphonate use. Most studies have focused on the risk associated with alendronate use, most likely because it was more widely used and was the first bisphosphonate approved (1995) in the US; it is unknown whether the other bisphosphonates would have a similar risk profile.

The observational studies all point to the fact that changes in bone morphology occur after exposure to bisphosphonates (cortical thickening). Whether these changes have any impact on fracture risk is unknown.

We determined the distribution of the bisphosphonates into the U.S. market using IMS Health's, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Data from Wolters Kluwer Source Lx® provides unprojected (i.e. non-national) patient counts with a medical and prescription claim for zoledronic acid. Our sample for this product was obtained from a small number of facilities: 30 clinics reporting medical claims and 40 pharmacies reporting the dispensing of a prescription. Therefore, due to the small sample size and the inability to characterize clinic or pharmacy information, there are limitations in the ability to identify national trends in the data. These data are not nationally projectable, therefore, we do not know how zoledronic acid and other injectable bisphosphonates are used nationwide.

Definition of atypical femoral fracture

Researchers attempting to translate the case report findings into a case definition to be used in epidemiologic studies were faced with an ICD-9 coding system which indicated the location of the fracture(see Figure 1) but which did not allow the determination of "atypicality". Therefore, studies conducted in administrative databases used study case definitions which differed slightly based on the types of data available for the specific study (medical records, claims, radiology, etc). Since there was no clear and consistent case definition for femoral fractures among the observational studies, the ability of researchers to design appropriate studies was hampered.

In September 2009, the American Society of Bone and Mineral Research (ASBMR) convened a Task Force to evaluate atypical subtrochanteric fractures seen with bisphosphonate use. The task force was asked to develop a case definition, conduct a literature review,

recommend diagnostic techniques, and recommend orthopedic and medical management. The task force recommendations, including the case definition, were published in November, 2010. The proposed case definition is summarized in table 1 below.

Table 1. Atypical Femoral Fracture: Major and Minor Features[a]

Major features[b]

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Noncomminuted
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.

Minor features

- _ Localized periosteal reaction of the lateral cortex[c]
- _ Generalized increase in cortical thickness of the diaphysis
- _ Prodromal symptoms such as dull or aching pain in the groin or thigh
- _ Bilateral fractures and symptoms
- _ Delayed healing
- _ Comorbid conditions (eg, vitamin D deficiency, RA, hypophosphatasia)
- _ Use of pharmaceutical agents (eg, BPs, GCs, PPIs)

[a]Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.

[b]All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures.

[c]Often referred to in the literature as beaking or flaring.

Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010;25:2267–2294. DOI: 10.1002/jbmr.253

Now that a firmly established case definition exists to evaluate the risk for atypical fractures, a study may now be designed to capture the defined elements of atypical fractures and address FDA's questions.

1. What is the incidence rate of subtrochanteric femoral fractures [atypical femoral shaft fractures] in the non-bisphosphonate exposed, post menopausal osteoporotic older population (male and female) in the United States?
2. What is the incidence rate of subtrochanteric femoral fractures [atypical femoral shaft fractures] in older populations taking bisphosphonates (male and female)?
3. What are the risk factors associated with developing subtrochanteric femoral fractures [atypical femoral shaft fractures] while on bisphosphonate therapy?
4. If the risk is greater among bisphosphonate users, is there an increased risk with duration of use?
5. Are older bisphosphonate users who stop use after a few years at lower risk of subtrochanteric femoral fractures [atypical femoral shaft fractures] than those who do not stop use?

While the establishment of the atypical fracture case definition is a solid step forward, a number of additional factors and possible research limitations remain. These include the need for a data source which includes sufficient numbers of patients with long term exposure, the ability to address confounding by indication, and the determination of the best method to measure the relative risk.

5 CONCLUSIONS

Whether there is an increased risk of low-energy femoral fractures in association with bisphosphonate use remains currently unknown. Existing observational studies to date have suggested but failed to definitively identify and measure the excess risk, if any. The current epidemiological literature concerning atypical femoral fracture was limited by the lack of a case definition which is difficult (or impossible) to apply in administrative databases without access to radiographs, insufficient power and limited follow-up. Further efforts to develop studies using the ASBMR definition in large populations with adequate documentation of drug exposure over long periods of time is warranted to provide evidence suitable for regulatory decision-making.

Table 1. Summary table of bisphosphonate drug products

Drug	Sponsor	Generics	Approval date	form	Indications	Dosing
Etidronate (Didronel)	Procter and Gamble	Y	9-1977	Oral Tab	Symptomatic Paget's disease of bone	5 to 10 mg/kg/day, not to exceed 6 months, or 11 to 20 mg/kg/day, not to exceed 3 months. May retreat after 90 days.
					Prevention and treatment of heterotopic ossification following total hip replacement	20 mg/kg/day for 2 weeks followed by 10 mg/kg/day for 10 weeks (12 weeks total).
					Prevention and treatment of heterotopic ossification following spinal cord injury	20 mg/kg/day for 2 weeks followed by 10 mg/kg/day for 10 weeks (12 weeks total)
Pamidronate (Aredia)	Novartis	Y	10-1991	injection	Hypercalcemia of Malignancy	60 to 90 mg as a intravenous infusion over 2-24 hours Retreatment only if clinically necessary
					Paget's Disease	30 mg daily, as a 4-hour infusion on 3 consecutive days Retreatment only if clinically necessary
					Osteolytic bone metastases of breast ca and osteolytic lesions of multiple myeloma	90 mg over a 2-hour infusion given every 3-4 weeks
Alendronate (Fosamax)	Merck	y	9-1995	Oral Tab/soln	Treatment and prevention of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis	*Treatment* • one 70 mg tablet once weekly *or* • one bottle of 70 mg oral solution once weekly *or* • one 10 mg tablet once daily *Prevention* • one 35 mg tablet once weekly *or* one 5 mg tablet once daily
					Treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density	*Men & women not taking estrogen* 5 mg tablet once daily, *Women taking estrogen* 10 mg tablet once daily.
					Treatment of Paget's	40 mg once a day for six months.

Ibandronate (Boniva)	Roche	None-tentative approval given	5/2003	Injection Oral Tabs	treatment and prevention of postmenopausal osteoporosis	• One 150 mg tablet taken once monthly *or* • one 2.5 mg tablet taken once daily
Risedronate (Actonel)	Warner Chilcott	None	3/1998	Oral tab	Treatment and prevention of postmenopausal osteoporosis (	Treatment 5 mg daily, 35 mg once a week, 75 mg taken on two consecutive days each month, *or* 150 mg once a month Prevention 5 mg daily, *or* 35 mg once a week
					Treatment to increase bone mass in men with osteoporosis	35 mg once a week
					Treatment and prevention of glucocorticoid-induced osteoporosis	5 mg daily
					Treatment of Paget's disease	30 mg daily for 2 months
Zoledronic acid (Zometa)	Novartis	none	8/2001	injection	Hypercalcemia of malignancy	4 mg as a single-dose IV infusion over no less than 15 minutes retreat with 4 mg after a minimum of 7 days
					Patients with multiple myeloma and patients with documented bone metastases from solid tumors Prostate cancer should have progressed after treatment with at least one hormonal therapy (1.2	4 mg as a single-dose intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of >60 mL/min
Zoledronic acid (Reclast)	Novartis	none	Reclast 4/2007 Zometa 2/2002	injection	Treatment of osteoporosis in postmenopausal women	5 mg infusion once a year given intravenously over no less than 15 minutes
					Prevention of osteoporosis in postmenopausal women	5 mg infusion given once every 2 years intravenously over no less than 15 minutes
					Treatment to increase bone mass in men with osteoporosis	a 5 mg infusion once a year given intravenously over no less than 15 minutes

					patients expected to be on glucocorticoids for at least 12 months	
					Treatment of Paget's disease of bone in men and women	a single 5 mg infusion given intravenously over no less than 15 minutes

Author	Year	Type	N*	#fx	Risk*	Advantage	limitations
Salminen[15]	2000	Cross sectional	202,592	201 fx w/ 50 low energy	Low energy fx: 9.9fx/100,000py	Identified low energy fractures	No assessment of drug use or osteoporosis status
Nevasier[13]	2008	Retro review of femoral fx (case series)	70	70	Alendr use predicted an atypical fx pattern OR 139.33 (19-934.4)	Assessed low energy fractures Reviewed x-rays	Does not address incidence ALE use confirmed in half of patients
Abrahamsen[1]	2009	Cohort and cross sectional	5,187	35/41	HR 1.46 (0.91–2.35, p = 0_12) Event rate of fx 1.1/1000 base 1.9/1000 expos	Medical records	No x-ray Long term use underpowered to conclusively assess risk No eval of transverse/spiral
Lenart[11-12]	8/2009	Case-Control	41 cases femoral fx		OR of bis use 4.44 [95% (CI) 1.77-11.35 OR of xray patterns OR, 15.33 [95% CI 3.06-76.90]; P < 0.001	Low energy femoral fractures Reviewed radiology	
Black[3]	2010	2º analysis	14,195	12	HR 1.03 (0.06-16.43) 1.5 (.25-9) 1.33 (.12 – 14.67)	Relatively large Looked specifically @ femur rx	No eval of confounding meds Underpowered to conclusively assess risk No x-ray
Nieves[14]	2010	Cross sectional using NHDS and administrative claims database			Incidence Nhds 53/100000py Claims 36/100000py (2006 data)	Utilized nationwide NHDS Attempted incidence definition	May miss non-hospitalized cases Does not assess atypical Diagnoses not validated No x-rays

FIT[?]	1998	RCT Placebo	2214 / 2218	227/182 other clinical fx	Rh 0.79 for other fx reduction		Did not assess femoral fractures (grouped as other)
Horizon[?]	2007	RCT placebo	3899 / 3876	19/84 other clinical fx	0.75 relative risk (RR) of non-vertebral fracture (95% CI 0.64-0.87) 0.67 RR of any clinical fracture (95% CI 1.28-0.77).		Femoral fracture not assessed (grouped as other)
Flex[?]	2006	RCT placebo	662/437	93/132	Non vertebral fx (RR 0.50, 95% CI 0.26-0.96) for low bmd women	Long term use Dose stratified	Femoral fracture not assessed (grouped as non-vertebral) Non-significant rr

*Active/control

APPENDIX 2: DRUG UTILIZATION TABLES

Table 1. Total number of dispensed prescriptions for the selected market by product form, strength, and gender in U.S. outpatient retail pharmacies, Years 2005-2009

	1/2005 - 12/2009							
	Female		Male		Unknown Gender		Total	
	TRx	*Horiz. Share*	TRx	*Horiz. Share*	TRx	*Horiz. Share*	TRx	*Share*
	N	%	N	%	N	%	N	%
Total Market	**139,338,139**	***92.4%***	**10,951,992**	***7.3%***	**495,264**	***0.3%***	**150,785,395**	***100.0%***
Alendronate sodium	**83,906,954**	***91.9%***	**7,087,834**	***7.8%***	**310,142**	***0.3%***	**91,304,931**	***60.6%***
TAB 70MG	69,746,237	*91.8%*	5,937,679	*7.8%*	264,885	*0.3%*	75,948,801	*83.2%*
TAB 70/2800MG	6,763,998	*93.0%*	496,184	*6.8%*	15,181	*0.2%*	7,275,364	*8.0%*
TAB 35MG	5,061,632	*92.5%*	393,892	*7.2%*	16,393	*0.3%*	5,471,917	*6.0%*
TAB 10MG	1,248,138	*89.0%*	144,881	*10.3%*	8,697	*0.6%*	1,401,716	*1.5%*
TAB 70/5600MG	471,253	*92.6%*	36,535	*7.2%*	958	*0.2%*	508,746	*0.6%*
SOLUT 70MG	414,058	*88.7%*	50,240	*10.8%*	2,566	*0.5%*	466,864	*0.5%*
TAB 5MG	195,435	*88.0%*	25,262	*11.4%*	1,437	*0.6%*	222,133	*0.2%*
TAB 40MG	6,202	*66.1%*	3,163	*33.7%*	25	*0.3%*	9,389	*0.0%*
Risedronate sodium	**39,082,114**	***92.5%***	**2,997,338**	***7.1%***	**162,925**	***0.4%***	**42,242,377**	***28.0%***
TAB 35MG	34,907,691	*92.5%*	2,659,941	*7.1%*	153,051	*0.4%*	37,720,683	*89.3%*
TAB 150MG	2,092,662	*93.1%*	152,511	*6.8%*	1,611	*0.1%*	2,246,784	*5.3%*
TAB 5MG	731,495	*90.3%*	73,435	*9.1%*	5,024	*0.6%*	809,954	*1.9%*
TAB 35/1250MG	558,294	*93.6%*	37,734	*6.3%*	726	*0.1%*	596,754	*1.4%*
TAB 30MG	435,995	*89.1%*	51,015	*10.4%*	2,234	*0.5%*	489,244	*1.2%*
TAB 75MG	355,976	*93.9%*	22,703	*6.0%*	279	*0.1%*	378,957	*0.9%*
Ibandronate sodium	**16,349,072**	***94.8%***	**866,820**	***5.0%***	**22,197**	***0.1%***	**17,238,088**	***11.4%***
TAB 150MG	16,272,118	*94.9%*	860,485	*5.0%*	21,981	*0.1%*	17,154,584	*99.5%*
INJECT 3MG	71,665	*92.1%*	5,951	*7.6%*	210	*0.3%*	77,825	*0.5%*
TAB 2.5MG	5,289	*93.1%*	384	*6.8%*	6	*0.1%*	5,679	*0.0%*

Source: SDI Vector One®: National, Data Extracted 3-2010. File: VONA 2010-588 bisphosphonates market strength_gender 3-29-10.xls

Table 2. Projected number of dispensed prescriptions for the selected market by patient age and gender (0-40, 41-49, 50-59, 60+) in U.S. outpatient retail pharmacies, 2005-2009

	2005		2006		2007		2008		2009	
	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share	TRxs	Share
	N	%	N	%	N	%	N	%	N	%
Total Market	**28,541,789**	***100.0%***	**30,960,238**	***100.0%***	**31,089,532**	***100.0%***	**31,142,717**	***100.0%***	**29,051,119**	***100.0%***
Alendronate sodium	**18,183,617**	***63.7%***	**18,304,862**	***59.1%***	**17,628,663**	***56.7%***	**18,296,059**	***58.7%***	**18,891,730**	***65.0%***
Age 0-40	163,251	*0.9%*	155,735	*0.9%*	141,743	*0.8%*	142,657	*0.8%*	131,678	*0.7%*
Female	112,818	*69.1%*	101,067	*64.9%*	87,661	*61.8%*	86,110	*60.4%*	82,023	*62.3%*
Male	48,734	*29.9%*	53,612	*34.4%*	53,320	*37.6%*	55,832	*39.1%*	49,160	*37.3%*
Unknown Gender	1,699	*1.0%*	1,056	*0.7%*	762	*0.5%*	715	*0.5%*	495	*0.4%*
Age 41-49	625,169	*3.4%*	539,744	*2.9%*	460,906	*2.6%*	432,946	*2.4%*	424,482	*2.2%*
Female	540,033	*86.4%*	458,588	*85.0%*	383,068	*83.1%*	355,628	*82.1%*	348,698	*82.1%*
Male	82,974	*13.3%*	80,169	*14.9%*	76,978	*16.7%*	76,234	*17 6%*	74,925	*17.7%*
Unknown Gender	2,162	*0.3%*	987	*0.2%*	860	*0.2%*	1,084	*0 3%*	858	*0.2%*
Age 50-59	3,744,921	*20.6%*	3,371,025	*18.4%*	2,961,576	*16.8%*	2,916,347	*15.9%*	2,932,862	*15.5%*
Female	3,520,483	*94.0%*	3,148,821	*93.4%*	2,749,020	*92.8%*	2,696,080	*92.4%*	2,700,896	*92.1%*
Male	215,603	*5.8%*	218,270	*6.5%*	208,856	*7.1%*	216,363	*7.4%*	227,987	*7.8%*
Unknown Gender	8,835	*0.2%*	3,934	*0.1%*	3,700	*0.1%*	3,904	*0.1%*	3,980	*0.1%*
Age 60+	13,561,682	*74.6%*	14,202,010	*77.6%*	14,033,780	*79.6%*	14,776,830	*80.8%*	15,385,272	*81.4%*
Female	12,558,086	*92.6%*	13,172,787	*92.8%*	12,994,232	*92.6%*	13,622,226	*92.2%*	14,125,321	*91.8%*
Male	920,093	*6.8%*	1,011,628	*7.1%*	1,028,540	*7.3%*	1,135,705	*7.7%*	1,240,192	*8.1%*
Unknown Gender	83,503	*0.6%*	17,595	*0.1%*	11,008	*0.1%*	18,899	*0.1%*	19,759	*0.1%*
Unknown Age	88,594	*0.5%*	36,348	*0.2%*	30,658	*0.2%*	27,279	*0.1%*	17,436	*0.1%*
Unknown Gender	57,225	*64.6%*	21,402	*58.9%*	18,206	*59.4%*	16,973	*62.2%*	10,542	*60.5%*
Female	25,878	*29.2%*	12,449	*34.2%*	10,552	*34.4%*	8,326	*30.5%*	6,103	*35.0%*
Male	5,491	*6.2%*	2,497	*6.9%*	1,900	*6.2%*	1,980	*7.3%*	791	*4.5%*
Risedronate sodium	**9,681,178**	***33.9%***	**9,461,361**	***30.6%***	**9,053,279**	***29.1%***	**8,057,207**	***25.9%***	**5,989,352**	***20.6%***
Age 0-40	92,519	*1.0%*	82,233	*0.9%*	68,655	*0.8%*	56,738	*0.7%*	37,290	*0.6%*
Female	69,050	*74.6%*	57,189	*69.5%*	45,590	*66.4%*	36,574	*64.5%*	25,958	*69.6%*
Male	22,940	*24.8%*	24,832	*30.2%*	22,951	*33.4%*	20,070	*35.4%*	11,207	*30.1%*
Unknown Gender	529	*0.6%*	212	*0.3%*	114	*0.2%*	94	*0.2%*	125	*0.3%*
Age 41-49	386,667	*4.0%*	316,789	*3.3%*	253,187	*2.8%*	202,915	*2.5%*	149,273	*2.5%*
Female	345,735	*89.4%*	279,745	*88.3%*	221,091	*87.3%*	173,847	*85.7%*	129,306	*86.6%*
Male	39,476	*10.2%*	36,550	*11.5%*	31,806	*12.6%*	28,860	*14 2%*	19,890	*13.3%*
Unknown Gender	1,456	*0.4%*	494	*0.2%*	290	*0.1%*	208	*0.1%*	77	*0.1%*
Age 50-59	2,143,626	*22.1%*	1,913,976	*20.2%*	1,645,605	*18.2%*	1,378,515	*17.1%*	1,083,958	*18.1%*
Female	2,033,943	*94.9%*	1,810,249	*94.6%*	1,549,658	*94.2%*	1,296,292	*94.0%*	1,021,637	*94.3%*
Male	105,743	*4.9%*	101,855	*5.3%*	94,600	*5.7%*	81,006	*5 9%*	61,649	*5.7%*
Unknown Gender	3,940	*0.2%*	1,872	*0.1%*	1,347	*0.1%*	1,217	*0.1%*	672	*0.1%*
Age 60+	6,983,040	*72.1%*	7,127,939	*75.3%*	7,072,024	*78.1%*	6,409,702	*79.6%*	4,713,545	*78.7%*
Female	6,471,697	*92.7%*	6,620,960	*92.9%*	6,564,550	*92.8%*	5,935,707	*92.6%*	4,365,212	*92.6%*
Male	475,739	*6.8%*	498,360	*7.0%*	502,095	*7.1%*	468,287	*7.3%*	344,427	*7.3%*
Unknown Gender	35,604	*0.5%*	8,619	*0.1%*	5,379	*0.1%*	5,708	*0.1%*	3,906	*0.1%*
Unknown Age	75,326	*0.8%*	20,424	*0.2%*	13,808	*0.2%*	9,337	*0.1%*	5,286	*0.1%*
Unknown Gender	61,262	*81.3%*	11,608	*56.8%*	9,148	*66.3%*	5,880	*63.0%*	3,164	*59.8%*
Female	11,739	*15.6%*	7,685	*37.6%*	3,989	*28.9%*	2,845	*30.5%*	1,867	*35.3%*
Male	2,325	*3.1%*	1,131	*5.5%*	671	*4.9%*	612	*6.6%*	256	*4.8%*
Ibandronate sodium	**676,994**	***2.4%***	**3,194,015**	***10.3%***	**4,407,590**	***14.2%***	**4,789,451**	***15.4%***	**4,170,038**	***14.4%***
Age 0-40	6,991	*1.0%*	29,875	*0.9%*	38,617	*0.9%*	38,864	*0.8%*	27,160	*0.7%*
Female	5,969	*85.4%*	24,006	*80.4%*	30,052	*77.8%*	29,617	*76.2%*	21,318	*78.5%*
Male	1,002	*14.3%*	5,809	*19.4%*	8,474	*21.9%*	9,128	*23.5%*	5,792	*21.3%*
Unknown Gender	20	*0.3%*	60	*0.2%*	91	*0.2%*	119	*0.3%*	49	*0.2%*
Age 41-49	36,387	*5.4%*	154,184	*4.8%*	181,557	*4.1%*	171,813	*3.6%*	128,952	*3.1%*
Female	34,179	*93.9%*	145,164	*94.1%*	169,345	*93.3%*	158,779	*92.4%*	117,496	*91.1%*
Male	2,171	*6.0%*	8,956	*5.8%*	12,065	*6.6%*	12,845	*7.5%*	11,358	*8.8%*
Unknown Gender	37	*0.1%*	64	*0.0%*	147	*0.1%*	189	*0.1%*	98	*0.1%*
Age 50-59	179,244	*26.5%*	847,859	*26.5%*	1,130,706	*25.7%*	1,177,964	*24.6%*	936,592	*22.5%*
Female	173,201	*96.6%*	820,664	*96.8%*	1,091,169	*96.5%*	1,136,498	*96.5%*	902,452	*96.4%*
Male	5,811	*3.2%*	26,567	*3.1%*	38,687	*3.4%*	40,520	*3.4%*	33,601	*3.6%*
Unknown Gender	232	*0.1%*	628	*0.1%*	850	*0.1%*	946	*0.1%*	538	*0.1%*
Age 60+	452,143	*66.8%*	2,158,500	*67.6%*	3,052,267	*69.3%*	3,396,623	*70.9%*	3,074,464	*73.7%*
Female	427,027	*94.4%*	2,047,604	*94.9%*	2,889,776	*94.7%*	3,209,774	*94.5%*	2,908,422	*94.6%*
Male	24,209	*5.4%*	109,123	*5.1%*	160,625	*5.3%*	184,335	*5.4%*	164,019	*5.3%*
Unknown Gender	907	*0.2%*	1,773	*0.1%*	1,866	*0.1%*	2,514	*0.1%*	2,023	*0.1%*
Unknown Age	2,229	*0.3%*	3,597	*0.1%*	4,443	*0.1%*	4,187	*0.1%*	2,872	*0.1%*
Unknown Gender	1,038	*46.6%*	1,471	*40.9%*	2,465	*55.5%*	2,475	*59.1%*	1,597	*55.6%*
Female	909	*40.8%*	1,738	*48.3%*	1,635	*36.8%*	1,241	*29.6%*	1,036	*36.1%*
Male	282	*12.7%*	388	*10.8%*	343	*7.7%*	471	*11.2%*	239	*8.3%*

Source: SDI Vector One®: National, Data Extracted 3-2010. File: VONA 2010-588 bisphosphonates age_gender 3-26-10.xls

Table 3. Projected number of patients by age and gender who filled a prescription for the selected market in U.S. outpatient retail pharmacies, 2005-2009

	2005		2006		2007		2008		2009	
	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*	Patient Count	*Share*
	N	%	N	%	N	%	N	%	N	%
Grand Total	**5,083,730**	***100.0%***	**5,640,382**	***100.0%***	**5,479,241**	***100.0%***	**5,696,298**	***100.0%***	**5,185,240**	***100.0%***
Alendronate sodium	**3,216,046**	***63.3%***	**3,363,691**	***59.6%***	**3,106,900**	***56.7%***	**3,457,096**	***60.7%***	**3,449,537**	***66.5%***
Age 0-40	45,173	*1.4%*	41,125	*1.2%*	35,009	*1.1%*	36,229	*1.1%*	31,132	*0.9%*
Female	33,501	*74.2%*	28,330	*68.9%*	23,362	*66.7%*	23,504	*64.9%*	20,849	*67.0%*
Male	10,741	*23.8%*	12,471	*30.3%*	11,380	*32.5%*	12,444	*34.3%*	10,131	*32.5%*
Unknown Gender	4,320	*9.6%*	1,407	*3.4%*	1,197	*3.4%*	950	*2.6%*	632	*2.0%*
Age 41-49	149,347	*4.6%*	130,952	*3.9%*	107,739	*3.5%*	103,295	*3.0%*	94,867	*2.8%*
Female	131,127	*87.8%*	113,776	*86.9%*	91,614	*85.0%*	86,656	*83.9%*	79,754	*84.1%*
Male	16,951	*11.4%*	17,010	*13.0%*	15,906	*14.8%*	16,271	*15.8%*	14,867	*15.7%*
Unknown Gender	6,171	*4.1%*	1,260	*1.0%*	1,268	*1.2%*	1,588	*1.5%*	1,370	*1.4%*
Age 50-59	725,098	*22.6%*	682,849	*20.3%*	583,461	*18.8%*	606,785	*17.6%*	584,000	*16.9%*
Female	680,501	*93.8%*	637,996	*93.4%*	542,111	*92.9%*	561,113	*92.5%*	539,342	*92.4%*
Male	41,377	*5.7%*	43,973	*6.4%*	40,564	*7.0%*	44,683	*7.4%*	43,647	*7.5%*
Unknown Gender	16,797	*2.3%*	4,273	*0.6%*	4,011	*0.7%*	4,781	*0.8%*	5,223	*0.9%*
Age 60+	2,319,218	*72.1%*	2,549,964	*75.8%*	2,414,285	*77.7%*	2,735,411	*79.1%*	2,680,487	*77.7%*
Female	2,134,942	*92.1%*	2,346,906	*92.0%*	2,217,221	*91.8%*	2,504,657	*91.6%*	2,448,192	*91.3%*
Male	173,600	*7.5%*	200,130	*7.8%*	195,246	*8.1%*	227,520	*8.3%*	228,859	*8.5%*
Unknown Gender	57,701	*2.5%*	13,659	*0.5%*	8,512	*0.4%*	14,905	*0.5%*	15,979	*0.6%*
Unknown Age	134,225	*4.2%*	115,772	*3.4%*	115,421	*3.7%*	129,625	*3.8%*	325,480	*9.4%*
Unknown Gender	61,802	*46.0%*	22,399	*19.3%*	18,124	*15.7%*	18,619	*14.4%*	11,435	*3.5%*
Female	100,324	*74.7%*	96,840	*83.6%*	98,508	*85.3%*	111,334	*85.9%*	292,960	*90.0%*
Male	9,938	*7.4%*	9,518	*8.2%*	9,268	*8.0%*	10,967	*8.5%*	29,563	*9.1%*
Risedronate sodium	**1,808,203**	***35.6%***	**1,806,707**	***32.0%***	**1,639,559**	***29.9%***	**1,546,897**	***27.2%***	**1,177,890**	***22.7%***
Age 0-40	26,458	*1.5%*	22,353	*1.2%*	17,370	*1.1%*	14,540	*0.9%*	9,910	*0.8%*
Female	20,857	*78.8%*	16,305	*72.9%*	12,249	*70.5%*	10,127	*69.6%*	7,208	*72.7%*
Male	5,279	*20.0%*	5,888	*26.3%*	5,064	*29.2%*	4,373	*30.1%*	2,671	*27.0%*
Unknown Gender	1,444	*5.5%*	576	*2.6%*	197	*1.1%*	101	*0.7%*	127	*1.3%*
Age 41-49	93,726	*5.2%*	78,487	*4.3%*	60,435	*3.7%*	48,918	*3.2%*	36,180	*3.1%*
Female	84,241	*89.9%*	70,268	*89.5%*	53,439	*88.4%*	42,543	*87.0%*	31,489	*87.0%*
Male	8,631	*9.2%*	8,123	*10.3%*	6,908	*11.4%*	6,316	*12.9%*	4,673	*12.9%*
Unknown Gender	3,769	*4.0%*	536	*0.7%*	479	*0.8%*	262	*0.5%*	83	*0.2%*
Age 50-59	427,072	*23.6%*	396,801	*22.0%*	329,410	*20.1%*	291,528	*18.9%*	227,419	*19.3%*
Female	404,877	*94.8%*	375,052	*94.5%*	310,207	*94.2%*	273,800	*93.9%*	213,700	*94.0%*
Male	21,050	*4.9%*	21,325	*5.4%*	18,907	*5.7%*	17,428	*6.0%*	13,573	*6.0%*
Unknown Gender	5,646	*1.3%*	1,952	*0.5%*	1,440	*0.4%*	1,401	*0.5%*	646	*0.3%*
Age 60+	1,267,003	*70.1%*	1,330,607	*73.7%*	1,251,099	*76.3%*	1,205,899	*78.0%*	888,264	*75.4%*
Female	1,169,333	*92.3%*	1,228,466	*92.3%*	1,153,813	*92.2%*	1,110,650	*92.1%*	818,622	*92.2%*
Male	92,923	*7.3%*	100,699	*7.6%*	96,419	*7.7%*	94,233	*7.8%*	68,798	*7.7%*
Unknown Gender	24,176	*1.9%*	6,536	*0.5%*	4,154	*0.3%*	4,822	*0.4%*	3,482	*0.4%*
Unknown Age	80,043	*4.4%*	57,366	*3.2%*	56,052	*3.4%*	50,892	*3.3%*	94,839	*8.1%*
Unknown Gender	62,721	*78.4%*	11,854	*20.7%*	9,134	*16.3%*	6,171	*12.1%*	3,334	*3.5%*
Female	50,759	*63.4%*	47,976	*83.6%*	47,932	*85.5%*	44,304	*87.1%*	85,943	*90.6%*
Male	4,991	*6.2%*	4,393	*7.7%*	4,273	*7.6%*	4,172	*8.2%*	8,033	*8.5%*
Ibandronate sodium	**319,494**	***6.3%***	**856,356**	***15.2%***	**1,026,103**	***18.7%***	**1,058,184**	***18.6%***	**870,883**	***16.8%***
Age 0-40	3,773	*1.2%*	10,616	*1.2%*	12,054	*1.2%*	11,301	*1.1%*	7,459	*0.9%*
Female	3,263	*86.5%*	8,721	*82.1%*	9,659	*80.1%*	8,844	*78.3%*	6,082	*81.5%*
Male	500	*13.3%*	1,879	*17.7%*	2,364	*19.6%*	2,411	*21.3%*	1,367	*18.3%*
Unknown Gender	21	*0.6%*	51	*0.5%*	94	*0.8%*	123	*1.1%*	51	*0.7%*
Age 41-49	18,141	*5.7%*	47,581	*5.6%*	52,213	*5.1%*	46,189	*4.4%*	32,957	*3.8%*
Female	17,102	*94.3%*	44,827	*94.2%*	48,744	*93.4%*	42,744	*92.5%*	30,253	*91.8%*
Male	1,018	*5.6%*	2,729	*5.7%*	3,421	*6.6%*	3,371	*7.3%*	2,683	*8.1%*
Unknown Gender	37	*0.2%*	73	*0.2%*	166	*0.3%*	274	*0.6%*	99	*0.3%*
Age 50-59	85,259	*26.7%*	232,307	*27.1%*	273,620	*26.7%*	272,564	*25.8%*	206,261	*23.7%*
Female	82,431	*96.7%*	224,493	*96.6%*	263,662	*96.4%*	262,135	*96.2%*	198,323	*96.2%*
Male	2,713	*3.2%*	7,621	*3.3%*	9,714	*3.6%*	10,172	*3.7%*	7,804	*3.8%*
Unknown Gender	246	*0.3%*	632	*0.3%*	959	*0.4%*	1,052	*0.4%*	538	*0.3%*
Age 60+	207,948	*65.1%*	573,028	*66.9%*	700,172	*68.2%*	741,526	*70.1%*	613,842	*70.5%*
Female	196,483	*94.5%*	541,795	*94.5%*	659,967	*94.3%*	697,868	*94.1%*	578,544	*94.2%*
Male	11,094	*5.3%*	30,819	*5.4%*	39,834	*5.7%*	43,153	*5.8%*	34,782	*5.7%*
Unknown Gender	781	*0.4%*	1,451	*0.3%*	1,473	*0.2%*	1,995	*0.3%*	1,783	*0.3%*
Unknown Age	8,304	*2.6%*	17,001	*2.0%*	21,978	*2.1%*	23,508	*2.2%*	57,311	*6.6%*
Unknown Gender	1,092	*13.2%*	1,561	*9.2%*	2,455	*11.2%*	2,687	*11.4%*	1,708	*3.0%*
Female	7,011	*84.4%*	15,042	*88.5%*	19,232	*87.5%*	20,562	*87.5%*	53,014	*92.5%*
Male	692	*8.3%*	1,207	*7.1%*	1,601	*7.3%*	1,821	*7.7%*	3,812	*6.7%*

APPENDIX 3: DATABASE DESCRIPTIONS

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Wolters Kluwer SOURCE Lx®

Wolters Kluwer Health's Source® Lx database a longitudinal patient data source which capture adjudicated claims across the United States from a mix of prescription claims from commercial plans, Medicare Part D plans, Cash and Medicaid claims. The database contains approximately 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients of which approximately 70 million patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis. The overall sample represents 27,000 pharmacies, 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

APPENDIX 4: REFERENCES

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Appendix 6: Staffa 2011 FDA Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 5, 2010
To:	Scott Monroe, M.D., Director, Division of Reproductive and Urologic Drug Products, OND
From:	Judy A. Staffa, Ph.D., R.Ph, Director (Acting), Division of Epidemiology, OSE
Subject:	A review of two observational studies of esophageal cancer in patients using oral bisphosphonates
Drug Name(s):	Alendronate, risedronate, ibandronate, etidronate, tiludronate
Submission Number:	N/A
Application Type/Number:	NDA 20-560, NDA 20-835, NDA 21-455, NDA 17-831, NDA 20-707
Applicant/sponsor:	Merck, Proctor & Gamble, Roche, Sanofi-Aventis
OSE RCM #:	2010-2077, Safety 000484, TSI #484

COVER MEMO

Attached are reviews from Dr. Diane Wysowski and Dr. Rita Ouellet-Hellstrom of two studies investigating the relationship between oral bisphosphonate (OBP) use and esophageal cancer. Both studies were conducted using the same data source, the General Practice Research Database (GPRD); however, the investigators used different methodologies which may account for their different findings. One study used a retrospective cohort design (Cardwell, et al) and the other a nested case-control design (Green et al). The cohort study did not find an increased risk (RR=0.96, 95% confidence interval 0.74-1.25); the case-control study did report an increased risk (RR=1.30, 95% confidence interval 1.02-1.66, particularly among patients dispensed 10 or more prescriptions (OR=1.93, 95% confidence interval 1.37-2.70).

Many types of design flaws can bias a study's results toward the null and Dr. Wysowski has appropriately identified some that could have biased the results of the Cardwell study toward not finding an association. However, case-control studies such as that conducted by Green are also tricky to design and analyze, and can be subject to many sources of bias as well. In her memorandum, Dr. Ouellet-Hellstrom has appropriately pointed out some important unanswered questions raised by both studies.

In my opinion, definitive conclusions about the risk of esophageal cancer associated with the use of OBPs cannot be made based on these two published studies alone, and unfortunately at this time, these are the largest, best-designed efforts available.

However, the signal generated by the Green study concerns me, and I am not reassured by the negative findings of the Cardwell study. The biological plausibility of the association, the widespread use of these products, and the unanswered questions about whether there are groups of patients that can be identified to be at increased risk are compelling reasons for exploring whether a more definitive study of this issue can be conducted. Dr. Ouellet-Hellstrom has nicely summarized characteristics of such a study. One of the key features would be stratification to assess interactions between OBP use and the presence of other gastrointestinal disorders (e.g. GERD, Barrett's disease) that are known or believed to be on the causal pathway to esophageal cancer. Neither of the current studies was able to definitively elucidate this potential interaction.

In the meantime, I think that enough evidence exists to support adding this information to product labeling and issuing a drug safety communication to alert practitioners and patients to this signal, and the accompanying uncertainty, to let them know that we continue to investigate it. This is a comparable strategy to that used across the Center when serious safety issues have been signaled in association with other commonly used drug classes. We in DEPI would be happy to continue to work with you to explore whether a more definitive study is feasible, given the rarity of the outcome of interest, the resultant need for large numbers of exposed patients, the complexity of teasing out the contribution of other risk factors along the causal pathway, and the need for lengthy patient follow up for detection of a cancer outcome.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	January 5, 2010
To:	Scott Monroe, M.D., Director, Division of Reproductive and Urologic Drug Products, OND
Thru:	Rita Ouellet-Hellstrom, Ph.D., Team Leader, Division of Epidemiology, OSE
	Judy Staffa, R.Ph., Ph.D., Acting Director, Division of Epidemiology, OSE
From:	Diane K. Wysowski, M.P.H., Ph.D., Epidemiologist, Division of Epidemiology, OSE
Subject:	A review of two observational studies of esophageal cancer in patients using oral bisphosphonates
Drug Name(s):	Alendronate, risedronate, ibandronate, etidronate, tiludronate
Submission Number:	N/A
Application Type/Number:	NDA 20-560, NDA 20-835, NDA 21-455, NDA 17-831, NDA 20-707
Applicant/sponsor:	Merck, Proctor & Gamble, Roche, Sanofi-Aventis
OSE RCM #:	2010-2077, Safety 000484, TSI #484

CONTENTS

EXECUTIVE SUMMARY

Two epidemiological studies were published in the summer of 2010 on the association between oral bisphosphonates and esophageal cancer in the U.K.'s General Practice Research Database (GPRD). One study led by Cardwell et al (1) used a retrospective cohort design and compared exposed oral bisphosphonate users to a control cohort (not all non-exposed) (1) and the other led by Green et al (2) used a nested case-control design (2). The former study reported no difference in the risk of esophageal cancer between the cohorts for any bisphosphonate use (adjusted hazard ratio, 1.07 (95% confidence interval, 0.77-1.49) and there was no difference in risk of esophageal cancer by duration of bisphosphonate use. The latter study found an increased incidence of esophageal cancer in people with one or more previous prescriptions for oral bisphosphonates compared to those with no such prescriptions (relative risk = 1.30, 95% CI, 1.02-1.66). Risk of esophageal cancer was significantly higher for 10 or more prescriptions (1.93; 95% CI, 1.37-2.70) than for one to nine prescriptions (0.93; 95% CI, 0.66-1.31) and for use over 3 years compared with no prescription (2.24; 95% CI, 1.47-3.43). In addition, the study by Green reported that risk of esophageal cancer in those with 10 or more bisphosphonate prescriptions did not vary significantly by age, sex, smoking, alcohol intake or body mass index; by diagnosis of osteoporosis, fracture, or upper gastrointestinal disease; or by prescription of acid suppressants, non-steroidal anti-inflammatory drugs, or corticosteroids.

The Division of Reproductive and Urologic Products (DRUP) asked the staff of the Division of Epidemiology (DEPI) to review these two studies and provide an evaluation of each study's strengths and weaknesses and offer explanations for the differing results. The text below provides this information in detail.

In summary, both studies shared common weaknesses in <u>not</u> having: validation of cancer diagnoses with medical records, information on histological diagnoses, information on risks of individual oral bisphosphonate drugs, complete data on risk factors for esophageal cancer, and information on use according to directions. Both studies noted that cancer diagnoses in GPRD have been shown to have a high rate of validity and that sensitivity analyses for the incomplete data on risk factors did not materially change the results. The other weaknesses would not be considered "fatal flaws."

However, the two studies were different in some important respects. Weaknesses of the study by Cardwell et al was its inclusion of exposed patients in the comparison group resulting in misclassification and lowering statistical power for analyses of exposed vs. unexposed, its shorter duration of subject follow-up, and its 1:1 matching of exposed to unexposed resulting in lower statistical power than the Green et al study. The observation time in the study by Green et al was almost twice as long as that in the study by Cardwell et al (on average, 7.7 years versus 4.5 years) and included people with longer durations of bisphosphonate use, which is critical for an analysis of drugs with cancer as an outcome. The study by Green et al also had greater statistical power to detect differences in oral bisphosphonate use between esophageal cancer cases and controls, with five matched controls per case compared with equal numbers in the exposed and comparison groups in the study by Cardwell et al. Moreover, when exposed

subject pairs were excluded from the comparison group in the Cardwell study, statistical power was jeopardized further.

Another important difference involved the definition of previous upper gastrointestinal disease which was an adjustment factor in the study by Cardwell et al and a stratification factor in the study by Green et al. Cardwell et al used a much more restrictive definition (only Barrett's esophagus and gastroesophageal reflux). Besides these two diagnoses, they excluded several diagnoses included by Green et al (esophagitis, hiatus hernia, esophageal ulcers, gastritis, duodenitis, peptic ulcers, and dyspepsia) that had an important effect in increasing risk as demonstrated in the Green et al study.

In addition, a key difference in the studies involved the data analyses. Green et al used stratification and Cardwell et al used adjustment of covariates. Stratification revealed that previous upper gastrointestinal disease diagnoses (some of which may be in the causal chain after use of a bisphosphonate) are important factors since, in the Green study, oral bisphosphonate use increased the risk for esophageal cancer from a statistically significant risk of 1.73 in those without previous upper GI diagnoses to 3.07 in those with previous upper GI diagnoses. The importance of a history of upper gastrointestinal disorders in association with esophageal cancer in the GPRD has been documented previously (3). Cardwell et al adjusted for Barrett's esophagus and gastroesophageal reflux disease, apparently diluting this important effect.

Therefore, the study design, methods, and analyses used by Green et al appeared to be more capable than those used by Cardwell et al of detecting a statistically significant association between oral bisphosphonate use and esophageal cancer and for demonstrating a duration-response effect of long-term oral bisphosphonate use.

Additional studies of the association between oral bisphosphonates and esophageal cancer conducted in independent databases are warranted.

1 BACKGROUND

In January, 2009, a case series describing reports submitted to the FDA of esophageal cancer in patients prescribed oral bisphosphonates was published in the *New England Journal of Medicine* (4). Since then, two large epidemiological studies on the association between oral bisphosphonates and esophageal cancer were recently published. They are summarized briefly in this section; more details are provided in sections 3.1 and 3.2 (below).

The first study published in *JAMA* in August, 2010 (1), found that between January, 1996, and December, 2006, in the U.K.'s General Practice Research Database (GPRD), 79 esophageal cancers were diagnosed in 41,826 persons prescribed oral bisphosphonates compared with 72 esophageal cancers diagnosed in 41,826 non-exposed persons, for an adjusted hazard ratio of 1.07 (95% CI, 0.77-1.49).

The second study published in *BMJ* in September, 2010 (2), determined that between 1995 and 2005 in the GPRD, 90 of 2,954 esophageal cancer cases were prescribed oral bisphosphonates one or more times compared with 345 of 14,721 controls without esophageal cancer for a relative risk of 1.30 (95% CI, 1.02-1.66; P = 0.02). Risk of esophageal cancer was significantly higher for those having 10 or more prescriptions (relative risk, 1.93; 95% CI, 1.37-2.70) than for those with one to nine prescriptions

(relative risk, 0.93; 95% CI, 0.66-1.31), and for those with use over 3 years than for those with no use (relative risk, 2.24; 95% CI, 1.47 to 3.43). Risk of esophageal cancer in those with 10 or more bisphosphonate prescriptions did not vary significantly by age, sex, smoking, alcohol intake or body mass index; by diagnosis of osteoporosis, fracture, or upper gastrointestinal disease; or by prescription of acid suppressants, non-steroidal anti-inflammatory drugs, or corticosteroids.

Of note, Green et al compared their results to those of Cardwell et al in the Discussion section of their article under the subheading, Comparison with other studies. They stated that in their study, the excess risk of esophageal cancer was largely restricted to people with 10 or more bisphosphonate prescriptions and to those with prescriptions over more than three years. In the study by Cardwell et al, people with equivalent length of exposure of 1,095 defined daily doses had an incidence of esophageal cancer of 6.6 per 10,000 person-years, while those with fewer defined daily doses had an incidence of 4.5 per 10,000 person-years giving an unadjusted relative risk for >1095 daily doses of 1.46 (95% CI, 0.78-2.60). Cardwell et al report an unadjusted relative risk of 1.08 (95% CI, 0.52-2.23) in bisphosphonate users with >1,095 defined daily doses compared with their matched controls. Green et al pointed out that for both of the estimates in the Cardwell study the confidence intervals are wide, and the relative risks are not significantly different from the relative risks in their own study with the more stable estimate of 2.24 (95% CI, 1.47-3.43) for more than 3 years versus no prescriptions. Green et al asserted that when broadly equivalent exposures are compared, the results from the two studies do not differ significantly.

However, in view of apparently different results of these studies, the FDA's Division of Reproductive and Urological Products (DRUP), Office of New Drugs, currently charged with the regulation of oral bisphosphonates, requested that staff of the Division of Epidemiology (DEPI), Office of Surveillance and Epidemiology, provide a critical review of the two studies. The consultation request specifically asked DEPI staff to answer six questions that are addressed in the review that follows.

2 MATERIALS REVIEWED

The following articles were reviewed:

1) Cardwell CR, Abnet CC, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of esophageal cancer. JAMA 2010;304:657-663 (1).

2) Green J, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of the oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ 2010;341:doi:10.1136/bmj.c4444 (2).

3 RESULTS

3.1 Synopsis of study by Cardwell et al

To investigate the association between oral bisphosphonate use and esophageal cancer, Cardwell et al extracted data from the U.K.'s GPRD to compare the incidence of esophageal and gastric cancer in a cohort of patients treated with oral bisphosphonates between January, 1996, and December, 2006, with incidence in a non-user control cohort. The researchers established an initial bisphosphonate cohort of all patients receiving a prescription for oral bisphosphonates during the 10-year study period. The date of the

first oral bisphosphonate prescription was taken as the index date. Participants were excluded from this initial cohort if they were younger than 40 years old on their index date or if they had a cancer diagnosis (excluding nonmelanoma skin cancer) in the 3 years prior to their index date.

Each bisphosphonate user was matched to a single control (who was allocated their index date) randomly selected from individuals of the same sex, year of birth, and general practice, regardless of bisphosphonate use. Therefore, some controls were members of the initial bisphosphonate cohort (with a later date of first bisphosphonate prescription than their match), but once selected as control participants they were excluded from the bisphosphonate cohort. In a sensitivity analysis, pairs of individuals were excluded in which the control was a bisphosphonate user.

Cancers were identified from relevant Read/Oxford Medical Information System codes in the patient's clinical files. Cox proportional hazards modeling was used to calculate hazard ratios and 95% confidence intervals for risk of esophageal and gastric cancer in bisphosphonate users compared with nonusers with adjustment for potential confounders.

The mean follow-up time was 4.5 and 4.4 years in the bisphosphonate and control cohorts, respectively. After excluding patients with less than 6 months' follow-up, 41,826 members in each cohort remained (81% women; mean age, 70 years). Seventy-nine esophageal cancers were diagnosed in the 41,826 persons prescribed oral bisphosphonates compared with 72 esophageal cancers diagnosed in the 41,826 control cohort (not all unexposed) for an adjusted hazard ratio of 1.07 (95% CI, 0.77-1.49). There was no difference in risk of esophageal and gastric cancer combined between the oral bisphosphonate and control cohorts (adjusted hazard ratio, 0.96; 95% CI, 0.74-1.25). There was no difference in risk of esophageal or gastric cancer by duration of bisphosphonate use.

3.2 Synopsis of study by Green et al

To examine the hypothesis that risk of esophageal, but not of gastric or colorectal, cancer is increased in users of oral bisphosphonates, Green et al conducted a case-control analysis in a cohort of patients prescribed oral bisphosphonates in the GPRD population. In 1995-2005, among men and women 40 years and older, 2,954 were diagnosed with incident invasive esophageal cancer, 2,018 with incident invasive gastric cancer, and 10,641 with incident invasive colorectal cancer. For each case, five controls (having no record of gastrointestinal cancer) before the index date (the diagnosis of the case) were matched for age (to within 2 years), sex, general practice, and observation period in the database. The mean observation period, identical by design for matched cases and controls, was 7.5 years on average. Conditional logistic regression was used to calculate relative risks of prior bisphosphonate use in cases versus controls and 95% confidence intervals adjusting for smoking status, alcohol intake, and body mass index.

The incidence of esophageal cancer was increased in people with one or more previous prescriptions for oral bisphosphonates compared with those with no such prescriptions (relative risk, 1.30; 95% CI, 1.02-1.66; P = 0.02). Risk of esophageal cancer was significantly higher for 10 or more prescriptions (1.93; 95% CI, 1.37-2.70) than for one to nine prescriptions (0.93; 95% CI, 0.66-1.31) (P for heterogeneity = 0.002). Risk was also significantly higher for use for over 3 years (on average, 5 years) compared with no

prescription (2.24; 95% CI, 1.47-3.43). Risk of esophageal cancer did not differ significantly by bisphosphonate type and risk in those with 10 or more prescriptions did not vary by age, sex, smoking, alcohol intake, body mass index; by diagnosis of osteoporosis, fracture, or upper gastrointestinal disease; or by prescription of acid suppressants, non-steroidal anti-inflammatory drugs, or corticosteroids. Cancers of the stomach and colorectum were not associated with prescriptions of oral bisphosphonates: relative risks for one or more versus no prescriptions were 0.87 (95% CI, 0.64-1.19) and 0.87 (95% CI, 0.77-1.00).

The authors concluded that oral bisphosphonates would increase the rate of esophageal cancer in individuals age 60-79 from 1 per 1000 population over five years to about 2 per 1000 with five years' use of oral bisphosphonates.

3.3 Major strengths and weaknesses of each study

Shared strengths

A major strength of both studies is the use of the GPRD as the source of their data. According to Cardwell et al (1), GPRD is the world's largest computerized database of longitudinal patient records without identifiers. Quality control of data exists because participating practices are trained and follow protocols to record and transfer data and the practices are assessed for completeness, continuity, and plausibility. Practices meeting pre-defined standards are registered as "up to standard." The information recorded includes demographic information, clinical diagnoses (classified using Read/Oxford Medical Information System codes), referral and hospital discharge information, and details of all prescriptions issued. The high quality of GPRD prescription and diagnosis information has been documented and a review of validation studies found that the median proportion of GPRD cancer cases confirmed (by general practice record request, algorithm, or manual review) was 95% (1). Indeed, a recent validation study of cancer diagnoses in GPRD performed by a DEPI colleague, Dr. Hui (Talia) Zhang, found a validation rate of 94% overall for cancer diagnoses (5).

Strengths of study by Cardwell et al

1) Stated that they included only "up-to-standard" practices of the GPRD

Investigators using GPRD can choose only "up-to-standard practices or all. Cardwell specifically stated that they only used these practices.

Weaknesses of study by Cardwell et al

1) Inclusion of exposed in the (unexposed) comparison cohort and resulting misclassification

Usually a cohort study compares exposed and unexposed for the frequency of the outcome. A weakness of this study is that the control cohort was randomly selected from individuals of the same sex, year of birth, and general practice (regardless of future bisphosphonate use) to compare with the exposed oral bisphosphonate users. Therefore, some controls were exposed to oral bisphosphonates although they "were members of the initial bisphosphonate cohort." The researchers then stated that once selected as control participants they were excluded from the bisphosphonate cohort. According to Table 1, 3,705 (9%) of *controls* had a bisphosphonate prescription during the study period.

It appears that the main analyses were conducted with these subjects included resulting in misclassification of exposed as unexposed. The researchers stated "a sensitivity analysis is presented excluding pairs of individuals in which the control was a bisphosphonate user." However, by excluding a large number of pairs, such a sensitivity analysis would have the important effect of reducing the study's statistical power.

2) Non-validation of cancer diagnoses

Cancer codes recorded for potential esophageal and gastric cancer cases were examined by a physician epidemiologist blinded to whether the patient was in the bisphosphonate or control cohort (a strength). However, according to the article, "Only patients with consistently recorded codes were accepted." The article reports that 27 cases had inconsistent codes and were not accepted. This could be a study weakness if actual cases were excluded or misclassified as noncases as a result. Rather than looking at codes for consistency, it would have been preferable to validate cancer diagnoses using the actual medical records.

3) Inadequate statistical power

The researchers used 1:1 matching. Had they used a larger number of matched controls (as Green et al did with 1:5 matching of cases and controls), the study's statistical power to detect a difference between the oral bisphosphonate cohort and the control cohort would have been increased.

4) Use of defined daily doses and tertiles to quantify exposure

The researchers extracted from the records "data on the preparations prescribed, the date of prescription, and the number of packs/tablets prescribed" and converted the data to "defined daily dose" (the assumed average maintenance dose per day). "The total number of DDDs of oral bisphosphonates received was divided by the number of days of follow-up and categorized by approximate tertiles into high, medium, and low use."

It is not clear why the researchers used defined daily dose to investigate dose response instead of the number of prescriptions and duration of use which are more easily understood measures than defined daily dose. Furthermore, it is not clear why the researchers chose to categorize defined daily dose as low, medium, and high rather than as a continuous variable.

5) Potential confounders missing and collected only from a 3-year period

In most medical record databases, information on common risk factors for cancer such as smoking, alcohol consumption, and body mass index are not systematically collected and recorded. The researchers document that for study subjects, 43%-50% had missing data on cigarette smoking and 63%-67% had missing data on alcohol use. The researchers state that body mass index was "opportunistically collected" within GPRD.

Furthermore, data on these and other risk factors (e.g., certain medications) were collected only within the 3-year period before the index date (the first oral bisphosphonate prescription). Consequently, because of missing risk factor data and an abbreviated period for collecting such data, misclassification of risk factors may be substantial.

6) Non-report of the number of subjects excluded with esophageal cancer within the first six months of follow-up

The researchers made the assumption that it was not possible for an oral bisphosphonate to have caused esophageal cancer within six months of use; therefore, they removed the first six months of follow-up for every participant. While their rationale seems reasonable, it would have been useful to know the number of esophageal cancer cases excluded for this reason. Furthermore, although such restriction lessens the possibility of detection bias, it also may lessen the opportunity to investigate oral bisphosphonates as a promoter of cancer.

7) Absence of information on mortality

No information is provided regarding the number of deaths due to esophageal or gastric cancer in the oral bisphosphonate and control groups in the study. I believe the number of fatalities due to esophageal cancer in each group should have been reported.

8) Exclusion of patients with cancer diagnoses in the 3 years prior to the index date

Cardwell et al excluded patients if they had a cancer diagnosis in the 3 years prior to their index date (start of bisphosphonate exposure and matched control). However, in most epidemiological studies of cancer outcomes, *any past diagnosis of cancer* (excluding nonmelanoma skin cancer) is an exclusion criterion for study entry because prior cancer is usually considered a risk factor for subsequent cancer.

9) Study period and shortened length of follow-up

The study period selected by Cardwell et al was from January 1, 1996, to December 31, 2006. The study was published in 2010. It would have been preferable had the researchers increased the study period to at least 2008, since longer follow-up is crucial for the identification of cancers that typically have relatively long latency periods.

As stated previously, 79 esophageal cancers were diagnosed in the 41,826 persons prescribed oral bisphosphonates compared with 72 esophageal cancers diagnosed in the 41,826 control cohort (not all unexposed) for an adjusted hazard ratio of 1.07 (95% confidence interval, 0.77-1.49). When the researchers tried to maximize follow-up by restricting analyses to patients whose first receipt of bisphosphonates was before January 1, 2000 (and their matched controls), the adjusted hazards ratio increased to 1.23 (95% CI, 0.66-2.30). Although not statistically significant (due to small numbers), it is noteworthy that the hazards ratio increased with longer duration of bisphosphonate use.

10) Incomplete definition of previous upper gastrointestinal disease diagnoses

Cardwell et al included diagnoses of Barrett's esophagus and gastroesophageal reflux disease (both before oral bisphosphonate use) as their definition of previous upper gastrointestinal disease. Green et al included many more diagnoses of previous upper gastrointestinal disease recorded before the first bisphosphonate prescription. These included esophagitis, gastroesophageal reflux disease, hiatus hernia, esophageal ulcers, Barrett's esophagus, gastritis, duodenitis, peptic ulcers, and dyspepsia. Therefore, the definition of previous upper gastrointestinal disease used by Cardwell et al was much more restrictive and excluded several diagnoses that appeared to have an important effect in increasing risk as demonstrated in the study by Green et al.

11) Adjustment for factors on the causal pathway

The adjustment by Cardwell et al for all known risk factors of esophageal cancer, including gastroesophageal reflux disease and Barrett's esophagus (that may be in the causal pathway of an esophageal cancer-oral bisphosphonate relationship) in their statistical model did not allow the evaluation of whether the risk factor was exacerbated by use of bisphosphonates. By using stratification for analyses, Green et al showed that oral bisphosphonate use in people with previous upper gastrointestinal disease substantially increased the risk of esophageal cancer. This finding is consistent with a previous study conducted in the GPRD in which a history of upper gastrointestinal disorders increased the risk of cancer (3).

12) Lack of information on histological diagnoses

As pointed out by the researchers, "the lack of information on histological subtype of esophageal cancers is also a weakness, and it is possible that an association with either esophageal adenocarcinoma or squamous cell carcinoma was obscured."

13) No information on bisphosphonate use according to directions

Esophagitis in oral bisphosphonate users has been associated with not taking them according to directions. The study could not examine whether this might be a risk for esophageal cancer because this information is likely not captured or coded in GPRD. The medical records or doctor's notes would have to be examined for any notation concerning use according to recommendations, and doctor's records would not have provided reliable and standardized data regarding adherence to prescribed directions.

Strengths of study by Green et al

1) Longer observation period than the study by Cardwell et al

The study period selected by Green et al was from 1995 to 2005 and the study was published in 2010. It would have been preferable had the researchers lengthened the study period to at least 2008. However, a major advantage of the study by Green et al was that the observation period for this study was, for both cases and controls, the period between the date of entry of the case into the GPRD and the date of diagnosis. Therefore, the observation period was longer for all cases and controls in the Green study regardless of bisphosphonate use compared to the one by Caldwell.

2) More statistical power than the study by Cardwell et al

For each case, Green et al selected five controls with no record of gastrointestinal cancer. Cardwell et al selected one control per exposed subject. The five controls per case conferred more statistical power that allowed for detecting a difference in oral bisphosphonate use between cases and controls.

3) Specificity of the results for esophageal cancer

Green et al did not find an association of oral bisphosphonate use with gastric cancer and colorectal cancer. The specificity of the association between oral bisphosphonates and esophageal cancer is one of the hallmarks of a true (nonrandom) association.

4) Analysis was restricted to those with at least 12 months' observation before the first bisphosphonate prescription

The restriction to those with at least 12 months' observation before the first bisphosphonate prescription allowed the researchers the assurance that the cases identified were new (incident) cases and allowed for documentation of medical history and risk factors.

5) Major findings rechecked using three sensitivity analyses

Green et al conducted three sensitivity analyses defining bisphosphonate exposure as two or more prescriptions; restricting analyses to patients with complete data on smoking, alcohol, and body mass index (complete case analysis); and restricting data on bisphosphonate prescription, smoking, and alcohol use to that recorded more than one year before the index date. Their results to these sensitivity analyses suggested that use of a multiple imputation method for dealing with missing data was not necessary in this dataset and may not be appropriate.

6) Data checked for detection bias

Green et al stated that to determine if bisphosphonate users were more likely to be investigated for upper gastrointestinal symptoms and thus be diagnosed as having early esophageal cancer, they performed an analysis restricted to people who died within a year of esophageal cancer (as they are less likely to have an early diagnosis). Although the data were not provided in the article, the investigators reported that the results were similar to the main analyses.

7) More comprehensive definition of previous upper gastrointestinal disease

Green et al included many more diagnoses of previous upper gastrointestinal disease recorded before the first bisphosphonate prescription than Cardwell et al did. These included esophagitis, gastroesophageal reflux disease, hiatus hernia, esophageal ulcers, Barrett's esophagus, gastritis, duodenitis, peptic ulcers, and dyspepsia. Therefore, the definition of previous upper gastrointestinal disease used by Cardwell et al (Barrett's esophagus and gastroesophageal reflux disease) was much more restrictive and excluded several diagnoses that appeared to have an important effect in increasing risk as demonstrated in the study by Green et al.

Weaknesses of study by Green et al

1) Lack of information on histological diagnoses

Similar to the study by Cardwell et al, the study by Green et al did not provide information on histological diagnoses.

2) No information on bisphosphonate use according to directions

Similar to the study by Cardwell, no information on bisphosphonate use according to directions was available.

3) No explanation offered about translating diagnosis codes from Read/OXMIS codes to ICD-10 codes

GPRD has a method for translating Read/OXMIS codes to ICD-10 codes. Apparently, this translation method was used but the researchers did not state this.

4) It appears that the study by Green et al stratified separately for various covariates and risk factors and did not provide a summary measure of association between oral bisphosphonates and esophageal cancer with all covariates adjusted in a multivariable model. It might have been informative to also provide an overall summary measure of association with adjustment for factors (excluding those believed on the causal pathway).

However, as stated previously, stratification (as opposed to adjustment) allows insight into the contribution of the bisphosphonate on the development of esophageal cancer. Since esophageal cancers occur predominantly in males and the known risk factors such as tobacco and alcohol use, obesity, and GERD explain a large proportion of the risk in the general population, an increase in a known risk factor (such as previous upper GI disorders) that possibly exacerbates or accelerates esophageal cancer in women may easily be missed when applying accepted statistical modeling.

3.4 Possible explanations of the different results of the studies

The possible explanations for the different study results include the longer observation period (mean of 7.5 years in cases and controls in Green compared with a mean of 4.5 years in exposed and 4.4 years in controls in Cardwell) and the greater statistical power (1:5 matching in Green compared with 1:1 matching in Cardwell) of the study by Green. In addition, the exclusion of 3,705 oral bisphosphonate-exposed pairs (because the controls were exposed) weakened the statistical power of the Cardwell study.

In addition, the differences in the definition of previous upper gastrointestinal disease diagnoses appears to have had an effect as well as the differences in analytic methods (stratification versus adjustment) that in the study by Cardwell et al appeared to hide an effect on cancer development of oral bisphosphonates in individuals with previous upper GI disease diagnoses.

3.5 Effect of the longer observation in study by Green et al

As mentioned previously, the longer the observation period and exposure, the greater the likelihood of detecting cancer that develops only after long-term exposure and a long latency period. The study by Green seems more favorable than that by Cardwell in its longer overall mean observation period of 7.5 years compared with 4.5 years, respectively, and in having the capability to show a duration-response effect.

3.6 Missing data for risk factors and impact on study validity

Both studies encountered missing data on covariates. Cardwell et al acknowledged this as a study limitation. However, they stated that the estimates seen in an analysis involving only participants with complete data on confounders were not different from those in the principal analyses.

Green et al stated that “data were available for most of the study participants on the main factors that have been associated with risk of oesophageal cancer, including smoking, alcohol intake, and body mass index. Adjustment for these minimized the scope for confounding by known risk factors, and sensitivity analyses that excluded participants with missing data on any of the adjustment variables gave results virtually identical to those in the overall analysis.”

Therefore, it would appear that the missing data had minimal impact on study validity for either study.

3.7 Adjustment for smoking and alcohol use

Cardwell et al adjusted data for smoking (never, former, current, missing), alcohol use (never, former, current, missing), and mean body mass index before the index date (first exposure). In addition to these covariates, they adjusted for use of hormone therapy (ever, before the index date), nonsteroidal anti-inflammatory drugs (ever, before the index date), H_2 receptor antagonists (ever, before the index date), proton pump inhibitors (ever, before the index date), and for diagnoses of Barrett's esophagus and GERD (ever, before the index date).

Green et al adjusted for smoking status (latest record before index date (cancer diagnosis): never, past, current, missing), alcohol intake (latest record before index date: non-drinker, drinker, missing), and body mass index (latest record at least two years before index date: <25, 25-30, ≥30, missing), diagnosis of osteoporosis or osteopenia within the observation period (yes, no), diagnosis of fracture (any site) recorded before the first bisphosphonate prescription (yes or no: analysis restricted to those with at least 12 months' observation before the first bisphosphonate prescription); diagnosis of upper gastrointestinal disease (including esophagitis, gastroesophageal reflux disease, hiatus hernia, esophageal ulcers, Barrett's esophagus, gastritis, duodenitis, peptic ulcers, and dyspepsia recorded before the first bisphosphonate prescription (analyses restricted to those with at least 12 months' observation before the first bisphosphonate prescription: yes or no), and prescription of non-steroidal anti-inflammatory drugs including aspirin, corticosteroids or acid suppressant drugs including H_2 receptor antagonists and proton pump inhibitors (yes or no: either at anytime during the observation period or before the first bisphosphonate prescription).

Green et al analyzed a more complete list of potential risk factors than did Cardwell et al. These included stratification for diagnoses of osteoporosis or osteopenia, a diagnosis of fracture, diagnosis of various upper gastrointestinal diseases, and use of corticosteroids. Inclusion of upper gastrointestinal diagnoses (which may be in the causal chain after use of a bisphosphonate) increased the risk for diagnosis of esophageal cancer from a statistically significant risk of 1.73 in those without upper GI diagnoses to 3.07 in those with upper GI diagnoses.

Which study had a higher frequency of misclassification of risk factors is not known and not knowable due to lack of standardized and complete data entered on medical records and in the GPRD database. Since esophageal cancer occurs predominantly in males and the known risk factors such as tobacco and alcohol use, obesity, and GERD explain a large proportion of the risk in the general population, an increase in a known risk factor that possibly exacerbates or accelerates esophageal cancer in women may easily be missed when applying accepted statistical modeling, as was done in the study by Cardwell et al.

3.8 Effect of relative risk versus odds ratio in study by Green et al

Odds ratios and relative risks are summary measures of association. Odds ratios are usually applied to describe the level of association or risk in case-control studies and

relative risks are used to describe the level of association or risk in cohort studies; however, odds ratios usually approximate relative risks. They are sometimes used interchangeably as summary measures of association. In any case, whether an odds ratio or a relative risk is calculated, the level of risk should be approximately the same.

4 SUMMARY

This review compared the study methods and results of two epidemiological studies conducted in the GPRD regarding the risk of esophageal cancer associated with the use of oral bisphosphonates (1,2). Study time periods overlap suggesting that some of the esophageal cases identified could have been included in both studies. Synopses of each study and an analysis of major strengths and weaknesses are provided. Although both studies had strengths and weaknesses, the study design, methods, and analyses selected by Green et al was able to detect a statistically significant association between oral bisphosphonate use and esophageal cancer and demonstrate a duration-response effect of long-term oral bisphosphonate use.

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From:	Rita Ouellet-Hellstrom Ph.D., M.P.H, Team Leader, Division of Epidemiology, OSE
Subject:	*Summary Overview for A review of two observational studies of esophageal cancer in patients using oral bisphosphonates*
Drug Name(s):	Alendronate, risedronate, ibandronate, etidronate, tiludronate
Application Type/Number:	NDA 20-560, NDA 20-835, NDA 21-455, NDA 17-831, NDA 20-707
Applicant/sponsor:	Merck, Proctor & Gamble, Roche, Sanofi-Aventis
OSE RCM #:	2010-2077, Safety 000484, TSI #484

Esophageal Cancer Epidemiology Summary

To better understand the two GPRD studies reviewed by Dr Wysowski, it is important to understand the epidemiology of esophageal cancer.

Esophageal cancer is an important public health problem worldwide. There are 2 major histological types: sqamous cell carcinoma (SCC) associated with environmental factors such as smoking and alcohol consumption, and adenocarcinoma (ADC) associated with Barrett's esophagus, gastroesophageal reflux (GERD), and increasing body weight. Both types are associated with a high mortality rate[1]. Barrett's esophagus is a metaplastic change of the esophageal lining where the normal sqamous epithelium is replaced by specialized intestinal columnar epithelium, a complication of GERD and, among other things, is an important risk factor for ADC.[2] Since these histological changes occur at the juncture of the lower esophageal and the upper gastric area, there is a concern that esophageal cancers could be misclassified as gastric cancer, hence the inclusion of gastric cancer in both studies reviewed, (Cardwell et al[3] separately and combined and Green et al[4] also includes colorectal cancer, all as separate groups).

A higher intake of fruit and vegetables, use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), exercise, and weight loss are associated with a lower risk of this cancer.

Esophageal cancer rates vary worldwide. Men have much higher incidence and mortality rates than women. The incidence and death rates for African American men have steadily declined over the past two decades but remain much higher than for white males although race has not been addressed in the two studies reviewed. This downward trend is not observed for other racial or ethnic groups. Among white males, the incidence of ADC rose since the mid-1970[5] but the overall esophageal cancer rate remains lower than for black males. Although over 80% of bisphosphonate users are women, the overall esophageal cancer incidence rates for women are at least 3 to 4 times lower than rates for men[6] (SEER 13:1992 and 2007) making testing any hypothesis of the potential carcinogenic effects of bisphosphonate exposure on the esophagus challenging at best. Nonetheless, there is biological plausibility for a bisphosphonate role in the development of esophageal cancer since its use has been associated with esophagitis, esophageal ulcers and esophageal erosions and there is evidence in the literature that esophageal cancer has been associated with chronic exposure to irritants, spices, hot drinks, alcohol and smoking[7] and GERD.

Published Studies

The two studies reviewed by Dr Wysowski and summarized in Table 3 were designed more or less successfully to address the concerns related above.

Green et al. identified the risk of bisphosphonate use among esophageal (ICD10 C15), stomach (C16) and colorectal (C18-20) cancer patients. Cases were matched on age (±2 years), sex, and time in GPRD) 1 case to 5 controls to increase power. These investigators also collected information on all important risk factors noted above but evaluated their effect using stratification rather than include them as covariates in the conditional logistic model.

Although the esophageal cancer cases consisted of 36% females, the investigators, reported on only bisphosphonate users which comprised 3.0 % of the cases and 2.3% of

the non-cases (a ratio of 1.3). Bisphosphonate use did not differ between cases and controls for gastric and colorectal cancers.

Nonetheless, these investigators did show an increased risk with duration of bisphosphonate use (< 3 years vs. 3+ years) and with the number of prescriptions (greater risk in 10+ prescriptions). In stratified analyses, the investigators compared bisphosphonate users having 10 or more prescriptions to all esophageal cancer cases who were non-users (all males and females). The stratified analyses did show that esophageal cancer risk estimates were higher in patients with longer bisphosphonate use, those with a prior diagnosis of upper gastrointestinal disease, in women, and in patients younger than 70 years of age.

Cardwell et al, on the other hand, used a bisphosphonate exposed/non-exposed cohort designed to assess the incidence of esophageal and gastric cancer using a Cox Proportional Hazards Model while adjusting for known risk factors. The investigators evaluated the risk of esophageal cancer as a sub-analysis. The cancer codes were not specified in the paper but the investigators noted that they were reviewed by an epidemiologist and only consistently recorded codes were accepted.

Of concern with this analysis is that if GERD is on the causal pathway to developing esophageal cancer, this analysis over adjusts and potentially would miss a bisphosphonate/esophageal cancer association that could be higher in GERD patients. An increase in GERD diagnosis among bisphosphonate users (12% of the exposed and 9% of the non-exposed had codes for GERD (a ratio of 1.34) prior to their index date (cohort entry) and that 0.47% of exposed and 0.35% of non-exposed (ratio of 1.34) had codes for Barrett's esophagus recorded) although the investigators noted that 1 control developed esophageal cancer. Dr Wysowski also mentions a potential lack of power and length of follow-up as two other potentially important deficiencies of this study.

Both studies matched for age and sex (Green at case identification and Cardwell at exposure identification) and adjusted for smoking, alcohol use, and BMI. Cardwell also included covariates for hormone therapy, NSAIDS, H_2 receptor antagonists, PPIs, Barrett's esophagus, GERD all before index date in the Cox Proportional Hazard model whereas Green evaluated the covariates separately.

Summary of Differences between Studies (see Table 3)

Similarities:

Both studies used the same database (GPRD), during almost the same time period (1995 to 2005 for Green and 1996 to 2006 for Cardwell), and captured the same covariates for adjustment or analysis but did differ on case definition.

Differences

Green et al identified esophageal (ES) cancer cases and matched each case to 5 non-cancer controls on age, sex, and time in GPRD and showed that (see Table 1)

1. The "risk" or probability of being a bisphosphonate user among esophageal cancer patients (64% males) was 3% for ES cases vs. 2.3% for non-case controls, a ratio 1.3.
2. Although length of follow-up for all cancers is 7.5 years, that for bisphosphonate users is 4.6 years.

3. Without modeling, the odds ratio and relative risk of bisphosphonate use among cases to that among controls equal 1.3.
4. When adjusted for smoking, alcohol use and BMI using conditional logistic regression the risk estimate was still 1.3 (also see table 2 in published report)
5. Although the analysis did not consider person-years of exposure, the investigators did match on length in GPRD.
6. Results separately show that when comparing all esophageal cancer cases to non-cases, the risk increases among
    - Those with a higher number of bisphosphonate prescriptions (≥ 10 prescriptions)
    - Those with a longer exposure to bisphosphonates (≥ 3 years)
    - Women
    - Younger ages (less than 70 years)
    - Those with upper gastrointestinal disease prior to index date (for cancer diagnosis)
7. The investigators analyzed esophageal, stomach, and colorectal cancers separately and showed lower risk of bisphosphonate use for the other two GI cancers.

Table 1 Odds Ratio and Relative Risks Estimates for Bisphosphonate Use (Green et al, 2010)

	All Esophageal Cancer		
Bisphosphonate Use	**Cancer Cases**	**Controls**	**Total**
Users	90	345	435
Non-Users	2,864	14,376	17,240
Total	2,954	14,721	17,675
Odds Ratio	*(90*14,376)*	*(345*2,864)*	*1.31*
Relative Risk (bisphosphonate)	*(90/2,954)*	*(345/14.721)*	*1.30*
Adjusted OR(Table paper2)			*1.30*
% of Prior Upper GI disease	*3.0%*	*2.3%*	*1.30*

Cardwell et al identified bisphosphonate exposed individuals and randomly matched (1:1) each exposed individual to only one non-exposed on age and sex and showed that (Table 2):

1. The risk of developing esophageal cancer among bisphosphonate exposed individuals compared to the-non exposed (81% Female).
2. Length of follow-up is 4.6 years for exposed and 4.4 years for the non-exposed.
3. The proportion of GERD and Barrett's esophagus was higher in bisphosphonate users than non users prior to the index date (cohort entry), a ratio of 1.34 although the investigators note that only 1 non-exposed eventually developed ES cancer.
4. When using the unadjusted Cox Proportional Hazard model, the hazard ratio for ES risk is 1.1 (note use of person-years of exposure) in model.
5. When adjusting for smoking, alcohol use, and BMI prior to cohort entry, the HR is reduced to 1.08.
6. When including known risk factors in model, the risk estimates are reduced to 1.07.

7. When the analysis combines ES with gastric cancer (primary analysis) the unadjusted HR using the Cox model is further reduced to 1.0 and the adjusted HR is 0.96.

Table 2. Odds Ratio and Relative Risks Estimates for Developing Cancer (Cardwell et al, 2010)

	Incident Esophageal* Cancer Cases		
Bisphosphonate Use	**Cancer Cases**	**Controls**	**Total**
Users	79	41,747	41,826
Non-Users	72	41,754	41,826
Total	151	83,501	83,652
Odds Ratio	*(79*41,754)*	*(72*41,747)*	*1.10*
Relative Risk (cancer)	*(79/41,826)*	*72/41,826)*	*1.10*
Adjusted OR(Table 3)			*1.08*
Prior GERD/Barrett's Dx	*12%/0.47%*	*9%/0.35%*	*1.34*

** The main analysis was for esophageal and gastric cancer combined but only esophageal cancer information is reported in this table*

Unanswered Questions

1. If GERD/Barrett's is a risk (as suggested by Green but controlled by Cardwell) is on the causal pathway, then Cardwell would have over adjusted in their analysis.
2. Given that ES cancers occur predominantly in males and that bisphosphonate users are predominantly female, an increase in the risk of bisphosphonate use in ES patients could easily have been masked by male risk factors for ES.
3. Although Green's study had more overall power, use of bisphosphonate was limited to only 3% of cases and 2.3% of non-cases with a median follow-up of 4.6 years (similar to Cardwell)
4. Finally, there is a question as to whether the case definitions were comparable
    - Green: esophageal (ICD10 C15), stomach (C16) and colorectal (C18-20) cancer patients
    - Cardwell: Only consistently recorded codes were accepted but codes were not specified in paper.

A definitive study that addresses the effect of bisphosphonate use on esophageal cancer development may be difficult to do given the low prevalence of esophageal cancer in women but would need to assess bisphosphonate use or misuse, the subsequent development of GERD/Barrett's Disease and its contribution on esophageal cancer. Such a study should include a long term follow-up of bisphosphonate initiators with no prior history of GERD. The outcome would be esophageal cancer incidence among those who develop GERD compared to those who do not develop GERD. Preferable, this study would be done in a US population to include a more representative racial distribution.

Table 3 – Design Summary (Sample)

	Green	Cardwell
3.1 Objectives/Aims/Scope		
3.2.1 Design		
3.2.1.1 Type	Nested Case-Control	Exposure Cohort
3.2.1.2 Data Source	GPRD	GPRD
3.2.1.3 Time Period	1995-2005	1996-2006
3.2.1.4 Criterion (Selection) Standards	Cancer cases & controls Male (64%) & Female (36%); 40+ years; 12 months of follow-up	Bisphosphonate exposed & non-exposed Male (19%) & Female (81%) 40+ years
3.2.1.5 PHI	N/A	N/A
3.2.2 Setting	MD Practice	MD Practice
3.2.3 Exposure/Intervention	Case – Incident, invasive esophageal, stomach, or colorectal CA 5Controls –No GI CA With at least 12 months of follow-up	Bisphosphonate Use Non-Exposed at index date (allowed future use of bisphosphonate to treat CA but excluded from bisphosphonate cohort)
Cancer definition	Incident invasive ICD 10 codes Esophageal - C15 Stomach – C16 Colorectal – C18-20	Incident cancer, codes not specified Reviewed by an epidemiologist. Only consistently recorded codes accepted
Matching	Match cancer case to non-cancer control 1:5; age ± 2 years, sex, practice, observation period in GPRD	Match bisphosphonate exposed to non-exposed 1:1; sex, year of birth, practice
Exclusions	Bisphosphonate use to treat Paget's disease & bone metastases	CA dx. In past 3 years; CA dx in 1st 6 months not counted
3.2.4 Outcome(s)	Bisphosphonate use (1+ prescription)	Esophageal & gastric CA
Mean follow-up	7.5 years overall average; 4.6 years for bisphosphonate use	4.5 yrs exposed 4.4 yrs non-exposed Max follow-up period 12.9 years
3.2.5 Covariates	• Smoking, alcohol, BMI (adj variables); • Stratified analyses on osteoporosis/osteopenia, fractures, upper gastrointestinal disease (esophagitis, GERD, Barrets etc), NSAIDS, H_2 receptors, steroids in 12 months prior to bisphosphonate use	• Smoking, alcohol, BMI in prior 3 years (adj. variables); • Hormone therapy, NSAIDS, H_2 receptor antagonists, PPIs, Barrett's esophagus, GERD all before index date
Censoring	None mentioned	Other CA dx, death, disenrollment or last data dump.
3.2.6 Sample Size	2,954 ES cases (90 users) 14,721 ES Controls (345 users);	41,826 users (79 EA) 41,826 non-users (72 EA) 80% power to detect 60% increase estimated
3.2.7 Statistical Analyses	• Conditional logistic regression; • Stratification on known risks for ≥ 10 prescriptions vs. no prescriptions. • Evaluated duration of use (time of last prescription – time of first prescription during observation period) • Missing data category included; • Sensitivity analyses	• Kaplan-Meier to assess proportional hazard; • Time to Event using Cox Proportional Hazard Model; • Missing data category included. • DDD for dose response
Software used	Stata 10.1	Stata 9.0 (5% level)

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01/06/2011

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Appendix 7: Voss 2011 FDA Review

Clinical Review

TSI #484: Bisphosphonates and esophageal cancer
Applications: NDA 20-560, NDA 20-835, NDA 21-455, NDA 17-831, NDA 20-707
Applicants: Merck, Warner-Chilcott, Roche, Sanofi-Aventis

Background

This safety application was initiated July 2, 2008, by the Division of Reproductive and Urologic Products (DRUP) and the Office of Surveillance and Epidemiology (OSE), in response to postmarketing reports of esophageal cancer in patients previously exposed to oral bisphosphonate (BP) drugs. Most of the reports have involved Fosamax (alendronate sodium), the most widely prescribed bisphosphonate, in patients treated for the indication of osteoporosis. Although BPs may have antineoplastic effects in some circumstances, their potential for esophageal mucosal irritation, and specifically a proposed analogy between BP esophagitis and reflux esophagitis, could provide plausibility for an association with esophageal cancer.

Esophageal squamous carcinoma, related to smoking and alcohol, has declined in incidence over the past 30-40 years. Esophageal adenocarcinoma, by contrast, has increased more than 6-fold in the U.S., in parallel to the rising prevalence of gastroesophageal reflux, which is believed to be due to factors such as obesity and the declining prevalence of *H. pylori*. Chronic acid reflux, in some patients, results in epithelial changes: columnar metaplasia of squamous epithelium, followed by intestinal metaplasia (i.e. "Barrett's esophagus"), followed by increasing dysplasia and adenocarcinoma. This sequence is believed to apply to almost all esophageal adenocarcinomas; no other mechanism of carcinogenesis is known. Gastric adenocarcinoma, by contrast, is etiologically linked in most cases to *H. pylori* infection (a lesser number of cases is related to autoimmune gastritis) and has been declining in incidence. Difficulty in classifying these malignancies may occur, as a large proportion of adenocarcinomas are located in the esophagogastric junction (EGJ) or "cardia" region, and local invasion present at the time of diagnosis makes their origin (i.e. esophageal vs. gastric) often unclear. In the absence of a clear defining criteria, the ICD system has historically classified all adenocarcinomas near the EGJ as gastric. However, many authors now believe that this assignation is incorrect, and that these malignancies are mostly if not all of esophageal origin.[1] This view is supported by epidemiologic data showing that EGJ adenocarcinomas are increasing in incidence over the past 30 years, similar to esophageal adenocarcinoma and the reverse of gastric adenocarcinoma; that they are associated with symptomatic reflux disease; and that they predominantly affect males. This evidence was recognized in 2009 by the American Joint Commission of Cancer (AJCC), which in its most recent Cancer Staging Manual classifies EGJ tumors as esophageal.[2]

No evidence from nonclinical studies or clinical trials has implicated oral BP exposure in esophageal carcinogenesis. In response to the initial reports (see below), Merck conducted a review of its data on alendronate relative to this issue. It was noted that 2 year rodent carcinogenicity studies showed no increase in esophageal or other GI tract malignancies, and that 3 year exposure in dogs did not result in hyperplastic or neoplastic changes in the esophagus. In alendronate clinical trials, a total of 2 patients had developed esophageal cancer:

- A 52 year old man entered a study of alendronate for Paget's disease. Ten days after beginning the drug, he developed pain, difficulty swallowing and vomiting; shortly thereafter an EGD revealed adenocarcinoma of the esophagus with metastases.

- A 57 year old man with CAD and history of prostate cancer, who had taken alendronate for 4 years, entered a trial of lipid lowering drugs; 3 months into the trial he was diagnosed with esophageal cancer.

Postmarketing Reports

The initial OSE review based upon AERS reports of esophageal cancer in patients exposed to oral BPs was communicated to the medical community via correspondence to NEJM in 2009.[3] There were 23 U.S. cases that followed BP exposure (all involving alendronate), and 31 cases from Europe and Japan that followed BP exposure (21 with alendronate, 10 with others). Most of the reports (74%) involved women, which differs from the strong preponderance of males with esophageal cancer; but this is not unexpected as ~90% of BP users are female. There was little information on known risk factors, except that 4 of the patients were noted to have Barrett's esophagus; this resulted in adding this condition to the Warnings and Precautions in oral BP labeling. The median time from initial BP exposure to cancer diagnosis was 2.1 years in the U.S. cases and 1.3 years in the others.

In follow-up to this initial report, Merck conducted a review (NDA 20-560, SD-508, submitted 4/9/09) of its worldwide safety database. A total of 62 cases of esophageal cancer, over a period of 13 years, were identified in patients who had received oral alendronate, which Merck believes includes the alendronate cases reported to NEJM. The median age was 70 y/o (range 30-88) and 73% were women. In the 42 cases in which there was enough information to estimate time from initial alendronate exposure to onset/diagnosis of cancer, the median latency was 20 months (range 5 days to 10 years). Latency exceeded 3 years in only 6 cases. Regarding predisposing factors, many of the 62 cases had a history of GERD or use of acid-reducing medications, and 4 had Barrett's esophagus. Cases in which cell type was reported included 12 with adenocarcinoma, 10 with squamous cell carcinoma, and 1 with undifferentiated carcinoma; in several cases, the narrative suggests the lesion was likely not an esophageal primary. Endoscopic findings in several cases note stricture or ulceration, which may indicate that obstruction to passage of alendronate tablet caused irritation which could have expedited detection of the cancer. There has been no secular trend in the number of these reports, either in absolute numbers or relative to estimated worldwide exposure. (**Table**) The latency period of this malignancy is unknown.

Table Postmarketing reports of esophageal cancer associated with alendronate‡

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
# of cases reported	2	4	11	7	5	5	4	4	7	4	2	3	4*	6**

‡ as reported to Merck
* covers only months of Jan-Feb 2009 (initial report to NEJM was 1/1/09)
Source: submission to NDA 20-560, SD-508, 4/9/09 except for:
**6 cases for reporting period Sept 2009-Sept 2010 reported in Nov 2010 PADER to NDA 20-560

Based on these reported cases, the cumulative worldwide reporting rate of esophageal cancer over this 13-year period was 0.13 per 100,000 patient-years of alendronate exposure. According to SEER data, the background incidence in U.S. adults age ≥ 65 years is 23.3 per 100,000 patient-years (37.5 per 100,000 among men and 11.2 per 100,000 among women).[4]

Epidemiologic studies
Prompted by the letter to NEJM, at least 6 research groups have investigated the possible association of esophageal cancer with oral BPs: 3 using data from the U.K. primary care General Practice Research Database (GPRD), 1 using the Danish national cohort, 1 using U.S. Medicare data, and 1 using the U.S. national VA database.

Green et al[5], using GPRD data, compared previous oral BP use in 2954 esophageal cancer patients, 2018 gastric cancer patients, and 10641 colorectal cancer patients, with 5 controls per case. The cases were matched for age, gender, general practice and observation time; analysis adjusted for smoking, alcohol and BMI. The odds ratio for BP exposure was increased for esophageal cancer patients (1.30, 95%CI = 1.02 to 1.66, p=0.02), and was not increased for either gastric cancer patients (0.87, 95%CI = 0.64 to 1.19) or colorectal cancer patients (0.87, 95%CI = 0.77 to 1.00). The esophageal cancer risk appeared even greater with a larger number of prescriptions or longer duration of use. Mean observation time between BP use and cancer diagnosis was 7.7 years.

Several weaknesses of this study, some of which have been observed by other authors[6] deserve mention. About half of the BP exposure in the esophageal cancer patients involved etidronate, a non-nitrogenated BP that has not been associated with esophagitis and therefore lacks the proposed biologic mechanism of carcinogenesis. The adjusted risk ratios for alendronate and risedronate individually were not statistically significant in the Green study, and there was no analysis done for these 2 drugs pooled together (i.e. excluding etidronate). Another factor is that case definition was by ICD-10 codes; as noted above, these may misclassify many EGJ tumors of esophageal origin as being gastric tumors. As noted by Pazianas[6], accelerated discovery of an esophageal tumor prompted by BP use resulting in an earlier EGD might assign more EGJ tumors correctly to the esophagus, relative to cancers in non-BP treated patients. This would help account for the higher esophageal but lower gastric cancer risk seen in BP users in the Green study. Another factor is that the case control design of this study resulted in an esophageal cancer study population that was 64% male, because of the male predominance of this disease; findings therefore may be of limited relevance to the overwhelmingly female population of BP users. A case control design also does not adequately address the issue of competing risks, which may be very significant in frail osteoporosis patients.

Cardwell et al[7] also used GPRD data in a retrospective cohort study. A total of 41,826 BP exposed patients and 41,826 controls were matched for age, gender and general practice. Unlike the Green study, 81% were female. After a mean follow-up time of 4.5 years, there were no differences between BP users and controls in risk of esophageal and gastric cancer combined (adjusted HR 0.96, 95%CI = 0.74 to 1.25), or in risk of esophageal cancer alone (adjusted HR 1.07, 95%CI = 0.77 to 1.49). Risk was also unaffected by type of BP (nitrogenated or non-nitrogenated alone, alendronate alone) or duration of use. Patients who took alendronate for more than 2 years had a HR for esophageal cancer of 0.85 (95%CI = 0.45-1.61). Neither this study nor the Green study validated diagnoses by review of primary patient records, or determined cell type (squamous cell vs. adenocarcinoma), which would be of great importance as these malignancies are pathogenetically distinct.

Merck, independently from the above groups, is sponsoring another study, limited to women, also in the GPRD database, conducted by Dr. Alec Walker of WHISCON LLC. Data were analyzed in both a case control and retrospective cohort manner. [redacted]. A validation study in a sub-sample, comparing electronic GPRD records to information in the primary patient charts, showed that in many cases, there was a delay of several months between the onset of symptoms or date of cancer diagnosis, and the entry of the diagnostic code into the GPRD. The investigator felt that this may cause inclusion of many cases in which the actual "latency period" was implausibly short. In addition, findings could be biased if patterns in recording diagnoses between different practices correlate with patterns of prescribing BPs. Therefore this investigation is continuing with chart abstraction in all cancer cases or possible cases, focusing particularly on date of clinical onset; chart review will also enable identification of the cancer cell type in most cases. This added information is not available in the other epidemiologic studies, which did not perform intensive chart review. Another report incorporating these additional data is tentatively set for submission in December, 2011.

Abrahamsen et al[8] evaluated a cohort of patients with fractures from the Danish national registers: 13,678 oral BP users and 27,356 non-BP users were matched for age, gender and fracture type. Over a median follow-up time of 2.2 years, BP users had significantly reduced risk for esophageal cancer (HR 0.35, 95%CI = 0.14 to 0.85, p=0.02) compared to controls. Risks for gastric cancer (HR 1.23; 95%CI = 0.68 to 2.22) and esophageal or gastric cancer combined (HR 0.78, 95%CI = 0.49 to 1.26) were not significantly different.

In a recent abstract[9] this group extended their analysis of Danish registry data in a larger cohort of 30,606 alendronate users (all women ≥50 y/o) and 122,424 matched controls. They found that endoscopy had been done in 4.1% of alendronate users in the year before treatment, compared to only 1.7% of controls (p<0.001). After a median follow-up time of 3.5 years on treatment, the HR for esophageal cancer was 0.73 (95%CI = 0.44 to 1.20) and for gastric cancer was 0.62 (95%CI = 0.39 to 0.98), adjusted for comorbidity (Charlson) and baseline endoscopy. Unlike the other studies, mortality was also examined: at 3 years, risk was significantly reduced for esophageal cancer death (HR 0.47, 95%CI = 0.23 to 0.96) and gastric cancer death (HR 0.49, 95%CI = 0.26 to 0.92). In a smaller subgroup with long term data (N=25,820), the 9 year risk of esophageal cancer death was HR 0.98 (95%CI = 0.51 to 1.80) and for gastric cancer death was HR 0.43 (95%CI = 0.19 to 1.03, p = 0.057).

Solomon et al[10] searched U.S. Medicare claims data of patients who were beginning osteoporosis treatments. Esophageal cancer incidence rates (per 100,000 patient-years) were 26.7 for patients receiving oral BPs and 48.4 for patients receiving other osteoporosis medications (e.g. raloxifene or calcitonin). The rate in oral BP users was not significantly different from SEER registry data for the ≥ 65 year age group (23.7 per 100,000 patient years).

Nguyen et al[11] limited their study to patients with pre-existing Barrett's esophagus, a population with esophageal adenocarcinoma risk that is ~30-125 -fold greater than the general population. In a cohort of 11,823 Barrett's patients identified in the Department of Veterans Affairs database,

116 patients who developed esophageal adenocarcinoma at least 6 months following diagnosis of Barrett's were matched with 696 controls who had Barrett's but did not develop cancer. Previous oral BP use (alendronate) was identified in 1.7% vs. 1.9% of cases vs. controls, with an incidence density ratio of 0.92 (95%CI, 0.21 to 4.15). The authors concluded that among patients with Barrett's esophagus, oral BPs did not increase the cancer risk. Weaknesses of this study are that 97% of cases were men, and that BP use was so uncommon: only 2 oral BP users developed cancer.

Discussion:
Evidence related to the putative association of oral BPs with esophageal cancer is difficult to evaluate, in part because of the large number of confounding factors which may introduce bias. For example, oral BPs may be preferentially prescribed for patients without GERD, which would tend to mask a tendency to increase esophageal cancer risk. On the other hand, it is likely that use of oral BPs leads to endoscopy with earlier detection of esophageal cancers in at least some patients. During 3-year alendronate clinical trials, 40-50% of subjects reported upper GI adverse events. In clinical practice, patients who are prescribed an oral BP are universally warned about GI problems. For patients who report such symptoms, the current standard of care in any patient > 45-50 y/o presenting with new upper GI symptoms (regardless of BP use), as recommended by numerous consensus panels, is to perform endoscopy; this procedure would be very unlikely to miss an existing neoplasm. A patient with a previously undetected esophageal tumor may be even more likely to experience symptoms due to the tumor causing obstruction to passage of a BP tablet, resulting in esophagitis and leading to an endoscopy.

Investigation of this issue was prompted by postmarketing reports of esophageal cancer in oral BP-exposed patients. However, these represent only ~1% of the estimated background rate of esophageal cancer, and have not been increasing over time. The extent of underreporting is unknown; Wysowski stated that rates of reporting of significant adverse effects of a drug are usually ~5-15%.[12] Reporting rates of esophageal cancer in oral BP patients would probably be higher than in other circumstances, because of awareness of the issue of esophagitis, and because some reports are initiated by attorneys related to litigation. The short latency period between BP exposure and esophageal cancer diagnosis (usually < 2 years) in most postmarketing reports is a major limitation: this would imply a mechanism involving not carcinogenesis but tumor promotion in high risk (i.e. Barrett's esophagus) patients, however one study showed that the risk of esophageal cancer in Barrett's patients was unaffected by previous oral BP use.

Of the 6 published epidemiologic studies of oral BPs and esophageal cancer, one appears to show an increased risk (approximately doubled), one shows a decreased risk (by approximately half), and 3 show no difference in risk. The remaining study is ongoing and will be the first to include intensive chart review, which may provide more detailed information such as cancer cell type.

Even if there is an association of oral BP exposure with esophageal cancer, the absolute risk would be low relative to the number of fractures prevented, including life-threatening hip fractures. According to SEER data, the background incidence of esophageal carcinoma in U.S. women age ≥ 65 years is 11.2 per 100,000 patient-years[4]; the worst-case estimate is that oral BP exposure may double this rate. For comparison, in osteoporotic women, ~700-1000 nonvertebral

fractures and ~1000-2300 clinical (symptomatic) vertebral fractures (per 100,000 patient-years) would be avoided by use of oral BPs.[13, 14]

Conclusion and Recommendations

Although studies are conflicting, it is very clear that there is not a marked increase in esophageal cancer risk with oral BPs. The issue of whether there is a slight increase in risk, or a reduced risk, may be difficult to resolve. One reason for the difficulty is that esophageal cancer is rare in women, particularly in relation to the risk of major fractures in those with PMO. Because oral BPs reduce fracture risk in this population by approximately half, and likely have no effect on esophageal cancer risk, the benefits of these drugs clearly continue to outweigh this and other potential risks. Even among men, who have higher baseline risk of esophageal cancer than women, this issue does not appear to significantly alter risk/benefit considerations.

The Office of Surveillance and Epidemiology has reviewed the studies of Green et al and Cardwell et al (memo to TSI #484 dated 1/5/11) and concluded that a Drug Safety Communication (DSC) should be issued to alert prescribers and patients of this possible safety signal, and that labeling changes are also warranted.

This reviewer believes that there are pros and cons concerning the need for a DSC at this time. The 2009 letter to NEJM served the purpose of alerting the medical community to this issue, as it alone has prompted at least 6 research groups to conduct studies to investigate further. The lay press has given much coverage to the issue as well. The evidence at this time does not appear to warrant any changes to BP prescribing or any other aspects of care in any subgroup of patients, thus it is unclear what benefit may derive from increased awareness of the issue; whereas there is great potential for negative effects including patient anxiety, inappropriate endoscopies, greater resistance to use of BPs for osteoporosis resulting in excess fractures with possible disability or death, or preferential use of more toxic alternative drugs. On the other hand, it is possible that these negative effects have already been occurring on some scale based on information disseminated thus far. A DSC will provide prescribers and patients with more detailed information to better inform decisions, and serve as a reminder that FDA continues to evaluate this issue.

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Appendix 8: Moeny 2011 (2) FDA Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Epidemiology Study Report

Date:	8-11-2011
Reviewer(s):	CDR David Moeny, MPH, R.Ph, USPHS Division of Epidemiology
Team Leader	Fatmatta Kuyateh, MD, MS Division of Epidemiology
Division Director	Judy Staffa, Ph.D, R.Ph. Division of Epidemiology
Drug Name(s):	Alendronate, etidronate, ibandronate, pamidronate, risedronate, tiludronate, zoledronic acid
Application Type/Number:	Alendronate (NDA 20-560 21-575) etidronate (NDA 17-831 019-545) ibandronate (NDA 21-455 21-858) risedronate (NDA 20-835) Tiludronate (NDA 20-707 zoledronic acid (NDA 21-817 22-080)
Applicant/sponsor:	Merck (alendronate), Novartis (zoledronate), Roche (Ibandronate), Warner Chilcott (risedronate)
OSE RCM #:	2010-588

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EXECUTIVE SUMMARY

Bisphosphonates are prescribed to lower the risk of osteoporosis related bone fractures. In recent years, a potential adverse effect of these drugs has been suspected to be atypical subtrochanteric and femoral fractures. These fractures are low energy (typically occurring from a standing height or less) and have a unique radiological presentation. Recent studies have found evidence that this risk may be associated with long duration of use. We obtained a dataset of new bisphosphonate users to examine the duration of use of bisphosphonate products among the retail pharmacy outpatient population.

Our study population consisted of 510,386 incident users of bisphosphonates; 91% were female, the median age at the first prescription of 67 years. For the patients receiving bisphosphonates approved for osteoporosis, approximately 49% of patients received 6 months or less of therapy, 64% received 1 year or less; approximately 2% of patients received therapy for 5 or more years. Patients who initiated therapy when they were age 35-60 years old tended toward shorter duration of use; approximately 58% of these patients received therapy for 6 months or less, 72% for 1 year or less, and 0.9% for 5 or more years. For patients who initiated therapy at age >60 years, 46% had therapy for 6 months or less, 61% for 1 year or less, and 2% for 5 years or more. The most commonly used osteoporosis approved product was oral alendronate 70mg, accounting for over half of the use in this population. Among patients over age 60 years, there appeared to be a higher percentage of long term users, (approximately 2% on 5 years of therapy or more) as compared to patients 35-60 years (approximately 1% with 5 years of therapy or more). Boniva 150mg was used more commonly among short term users (23.1% vs. 14.3% at therapy initiation); most likely due to the more recent approval of this product. There were no other substantial differences between long term users, compared to short term users (less than 5 years of therapy), other characteristics for which data were available.

1 INTRODUCTION

The occurrence of atypical femoral fractures has been identified as a potential adverse event associated with the use of bisphosphonates. The recent completion of a consensus statement by the American Society for Bone and Mineral Research, which provided a definition for atypical femoral fractures, and the completion of several new epidemiologic studies have raised the question of whether one of the risk factors for these fractures might be the duration of bisphosphonate therapy. To provide context for regulatory decision making, and for an upcoming advisory committee meeting, this review presents the results of duration-of-use analysis conducted in a large U.S. prescription claims database.

1.1 BACKGROUND

Bisphosphonates are prescribed for the treatment and prevention of osteoporosis. This class of drugs is widely used and has proven to be effective at reducing the

incidence of fracture, a significant cause of mortality among the elderly (2, 6). During 2009, 10% of women and 1% of men over age of 55 years of age received a bisphosphonate drug through U.S. outpatient retail pharmacies(11). Rare but serious side effects have been reported in patients on bisphosphonate therapy, including atypical femoral and subtrochanteric fractures and osteonecrosis of the jaw.

A number of case series have been published over the last 6 years describing unusual femoral fractures in patients taking bisphosphonate drug products (1, 3-5, 7-9, 17, 19). These unusual fractures have come to be classified as atypical subtrochanteric and diaphyseal femoral factures (13). These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.

Recent research has begun to focus on whether the duration of bisphosphonate use impacts the risk of atypical femoral fracture. Several studies have been published showing an increase in the risk of fractures for patients who exceed 3-5 years of therapy, leading some authors to suggest that patients should be evaluated for therapy exceeding 5 years(12-16, 18). At this time, there are no diagnostic codes which specifically identify atypical fractures. However, several studies have provided evidence that long-term use of bisphosphonates may be a risk factor for subtrochanteric and diaphyseal femoral fracture (10) (1).

1.2 REGULATORY HISTORY

The first bisphosphonate approved for the treatment of postmenopausal osteoporosis was Fosamax (alendronate sodium) in 1995. Actonel (risedronate sodium), Boniva (ibandronate sodium), and Reclast (zoledronic acid) were approved in 2000, 2003, and 2006 respectively. On 10/13/2010, the FDA issued a drug safety communication stating that atypical subtrochanteric and diaphyseal fractures are a rare outcome accounting for less than 1% of overall hip and femur fractures and that these fractures may be related to long-term use of bisphosphonates. An advisory committee meeting to discuss the risk for atypical fractures, other potential long-term safety issues and long-term efficacy of bisphosphonates for the prevention and treatment of osteoporosis is scheduled for September 2011.

2 METHODS AND MATERIALS

Nationally projected estimates of the quantity of bisphosphonates sold in the wholesale market were obtained from IMS Health's National Sales Perspectives™ for the calendar years 2008-2010. The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. For this analysis, sales volume is expressed in terms of the number of "eaches" (the number of bottles, vials, or IV bags sold). Outlets within the retail market include the following pharmacy settings: chain drug

stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

A dataset of bisphosphonate prescriptions was obtained from the SDI Vector One data warehouse. Vector One® integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients. Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Prescriptions for the entire class of bisphosphonates (USC 59211) were obtained for the years 2005 – 2010. To provide assurance that the patients contained within the dataset were likely to have been followed for the entire time period, we applied pharmacy stability and patient eligibility controls prior to dataset delivery. Pharmacy stability controls assure that all pharmacies represented in the dataset reported consistently throughout the entire study period (i.e. were in business and filling prescriptions which were captured by SDI). Patients were eligible for inclusion in the dataset if they had a prescription filled for any drug product (not just a bisphosphonate) during three 6 month periods: January – June 2005, at the midpoint of the study period, and July-December 2010.

We examined duration of use beginning January 1, 2006. The study was restricted to incident users: those with a first prescription on or after January 1, 2006 with no previous prescription for a bisphosphonate in the prior year.

Duration of use was characterized using two measures: the sum of the total days supply dispensed, and the sum of all episodes of bisphosphonate use. Prescription fills which occur within the period of the days supply plus a 25% grace period of the previous prescription is included in the current episode. Prescription fills occurring early (i.e. prior to the end date of the previous prescription) are added to the end of the previous prescription. Two examples of episode construction are provided as figure 1 in the appendix.

Duration of use was examined in two cohorts: patients receiving one or more of the bisphosphonates approved for osteoporosis diagnoses (alendronate, ibandronate, risedronate, zoldronic acid-Reclast) and patients receiving one or more of any bisphosphonate.

3 RESULTS

3.1 NATIONAL DRUG DISTRIBUTION DATA

Outpatient pharmacies accounted for the majority of the distribution of the bisphosphonates approved for osteoporosis diagnoses (Appendix Table 1). For the years 2008-2010, mail order and traditional retail pharmacies accounted for roughly 85% of the number of bottles of alendronate, risedronate, and ibandronate sold. Zoledronic acid is primarily distributed to non-retail channels (i.e. hospitals, clinics, HMOs, etc.); these distribution channels accounted for roughly 97% of the vials / intravenous bags sold. Among all bisphosphonates approved for osteoporosis, alendronate had the highest sales volume, accounting for 70% of the total wholesale sales volume during 2010.

3.2 DURATION OF USE

The dataset retrieved from SDI contained 919,932 patients. After data cleaning and removal of prevalent users (detailed in Appendix Table 2), there were 369,156 patients in the prescription claim study population who received only bisphosphonates approved for osteoporosis; there were 510,386 patients who received any bisphosphonate (Table 1). Females accounted for the majority of the utilization of bisphosphonate products, accounting for approximately 91% of patients in each cohort. The median age at the first episode of bisphosphonate therapy was 67 years; approximately 70% of the study population was older than 60 years of age. The osteoporosis therapy cohort and the all-drug cohort were similar in terms of patient demographics.

Table 1. Demographics of bisphosphonate study population, SDI Vector One, 2006-2010.

	Osteoporosis Bisphosphonates		All Bisphosphonates	
	# Individuals		# Individuals	
	N	%	N	%
Total	369,156		510,386	
Gender				
Female	334,220	90.5	463,042	90.7
Male	34,899	9.5	47,290	9.3
Unknown	37	0.0	54	0.0
Age				
median (interquartile range)	67	19	67	18
35-60	106,611	28.9	150,199	29.4
> 60	262,545	71.1	360,187	70.6

For the population dispensed bisphosphonates approved for prevention and treatment of osteoporosis, the median number of bisphosphonate prescriptions dispensed per patient was 5, with a median of 28 days supply per prescription; the

mean number of prescriptions and days supply per prescription were 10.1 and 36.7, respectively (Table 2). The median total prescription days supply that a patient received was 198 days, and the mean was 380.4 days. The cohort had a median of 2 episodes of therapy, for a median total duration of 196 days. The mean number of episodes per patient was 2.7 with a mean total duration of 380.4 days of therapy. The results of the analysis when including users of any bisphosphonate products were similar.

Table 2. Key utilization measures of bisphosphonate use – SDI Vector One, 2006-2010

	Osteoporosis Bisphosphonates			All Bisphosphonates		
	Median	Mean	Std Dev	Median	Mean	Std Dev
Prescriptions per individual	5	10.1	12.1	5	10.6	12.5
Days supply per prescription	28	36.7	20.2	28	36.2	19.7
Days supply per patient	196	380.4	450.0	200	392.3	451.1
Prescriptions per episode	1	3.8	6.1	1	3.7	6.1
Episodes per individual	2	2.7	2.8	2	2.9	2.9
Therapy days per episode	59	140.6	225.9	57	137.1	223.0
Total duration per individual(days)	198	388.3	459.2	207	400.5	460.3

A distribution of the total duration of use by the number of months of therapy for the population using using bisphosphonates approved for osteoporosis is provided in Appendix Figure 2. Approximately 49% of patients received 6 months or less of therapy, 64% received 1 year or less; approximately 2% of patients received therapy for 5 or more years. Patients who initiated therapy when they were age 35-60 years old tended toward shorter durations of use (Appendix Figure 3); approximately 58% of these patients received therapy for 6 months or less, 72% for 1 year or less, and 0.9% for 5 or more years. For patients who initiated at age >60 years (appendix, Figure 4), 46% had therapy for 6 months or less, 61% for 1 year or less, and 2% for 5 years or more.

Use of bisphosphonates indicated for osteoporosis is concentrated in older patients. We examined the duration of use in this cohort stratified into two age categories: age 35-60 and over age 60 at initiation of bisphosphonate treatment. Patients who were over age 60 years had a longer median duration of therapy (224 days) than those aged 35-60 years (140 days) (Table 3). The mean total duration of therapy was 303.1 days and 417.4 days, respectively.

Table 3. Duration of use for osteoporosis bisphosphonates, by age at therapy initiation

	Age 35-60 Years			Age > 60 years		
	Median	Mean	Std Dev	Median	Mean	Std Dev
Total days supply	140	296.9	374.0	224	408.8	469.7
Episodes per individual	2	2.7	2.7	2	2.8	2.8
Total duration per individual	144	303.1	381.7	230	417.4	479.3

We further examined the patients using a bisphosphonate approved for osteoporosis for 5 years or more compared to those with less than 5 years of therapy. The cohorts were similar with respect to patient sex. Compared to patients with less than 5 years of therapy, those with 5 or more years of therapy were more likely to have MediCare reimbursement, and less likely to have third party insurance or pay in cash (Appendix Table 3). We did not see any substantive differences between shorter and longer term users with regard to specialty of prescribing physician at therapy initiation (Appendix Table 4). The product most commonly used at initiation of therapy was Fosamax 70mg or the generic equivalent alendronate 70mg (Appendix Table 5). Long term users initiated therapy with one of these products 65.9% of the time, while short term users initiated with these products 62.7% of the time. Although the numbers of patients receiving the product is low, Boniva (ibandronate) 150mg use was more common among short term users compared to long term users (23.1% vs. 14.3%); most likely due to the more recent approval of this product. The comparison of the product type for the final prescription received was similar, with the exception that generic alendronate 70mg alone accounted for 54.6% of short term users, and 73.5% of long term users (Appendix Table 6).

4 COMMENTS/DISCUSSION

In our analysis of retail pharmacy claims data, a small proportion of bisphosphonate users received bisphosphonate therapy for 5 or more years. This analysis is highly dependant upon the days supply field, which is populated by the dispensing pharmacist. A quality check of the days supply dispensed data field revealed that some prescriptions appeared to have the days supply incorrectly coded based on the approved drug dosage. For example, nearly all zoledronic acid prescriptions were coded for 30 days, when the product is labeled for once or twice yearly dosing. We conducted a sensitivity analysis examining the impact of correcting the days supply variable to standard approved dosing. A corrected days supply was calculated for the bisphosphonates approved for osteoporotic indications (alendronate-Fosamax, ibandronate-Boniva, and zoledronic acid- Reclast) based on the approved dosing for each drug formulation and strength. Zoledronic acid is approved for both yearly and bi-annual dosing; the actual median days between prescription fills (357 days) was used as the corrected days supply value. For the 3,988,902 prescriptions for osteoporosis drug products, we identified 959,801 where the ideal days supply based on approved dosing did not match the reported days supply. The median difference between the corrected days supply and the original days supply (corrected-original) was 2 days, the mean was 30.4 days. The duration of use analysis was conducted using both the corrected and the uncorrected value. Bisphosphonates approved for indications other than osteoporosis have dosing instructions which are often based on clinical criteria. Therefore, the calculation of a corrected days supply for non-osteoporosis bisphosphonates is impossible using prescription claims data. For these products, the original, uncorrected days supply value was used. The impact of these

corrections on the total duration of therapy was negligible, only increasing the total duration length by 1 or 2 days.

While we attempted to examine differences between long term users and short term users, given the data elements available to us in our prescription claims database, the differences noted were most likely due to the age at product initiation and the availability of the products in the marketplace at the time of initiation.

The limitations of this analysis include the inability to determine the indication for use as osteoporosis/osteopenia or other indications, therefore we had to assume that products approved specifically for osteoporosis prevention and/or treatment were actually being used for that indication. The ability to capture patients using injectable products through our retail pharmacy claims database is limited, thus our analysis likely under-represents the contribution of these patients to an overall duration of use estimate. Our examination of sales data suggests, however, that bisphosphonates are predominantly sold into retail settings, even the injectables, so it is not likely that we are missing a large percentage of patients. Additionally, the inclusion criteria of any prescription activity within the first and last 6 months of the study period may eliminate patients who receive the injectable formulation who have no other chronic medications, as well as those who were previously not receiving any drug prescriptions, but initiated bisphosphonate therapy during the analysis period. The effect of applying these patient eligibility criteria, however, would be expected to decrease the proportion of patients on long term bisphosphonates, which is already quite small. While there appeared to be differences between long term and short term users, statistically testing was not conducted to confirm these findings. Finally, this analysis is based on pharmacy transactions and we are unable to determine actual patient behavior (i.e. whether the medication was actually taken).

Other databases often rely primarily on adjudicated insurance claims, which have high levels of patient turnover due to the frequency at which commercially insured patients change jobs or insurance plans. In contrast, this retail pharmacy claims database is likely to have a lower turnover of the patient population, allowing the ability to capture longer term use. In addition, these data are likely to be more representative of the country as a whole due to the inclusion of patients receiving medication paid for in cash, patients covered by Medicare, and patients without commercial insurance. However, we are unable to determine for certain whether we captured all of a patient's prescription activity throughout the entire study period since there are no "enrollment" data in retail pharmacies. In addition we do not know whether these data are truly nationally representative.

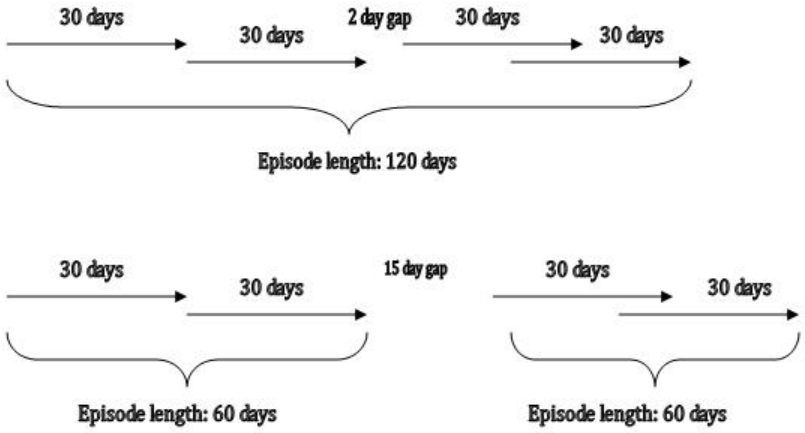
5 CONCLUSIONS

In this analysis, we determined that patients receiving long-term bisphosphonate therapy (5 or more years) represent a minority of all bisphosphonate exposed

patients. Patients receiving 5 or more years of therapy constitute approximately 2% of the patients in this sample. In both long term and short term (less than 5 years) users, alendronate 70mg was the most commonly used product. Boniva 150mg was used more commonly among short term users (23.1% vs. 14.3% at therapy initiation); most likely due to the more recent approval of this product. Among patients over age 60 years, there appeared to be a higher percentage of long term users, (approximately 2% on 5 years of therapy or more) as compared to patients 35-60 years (approximately 1% with 5 years of therapy or more). There were no other substantial differences between long term users, compared to short term users (less than 5 years of therapy), other characteristics for which data were available.

APPENDICES

Appendix Figure 1. Episode construction using a days supply plus 25% grace period definition



Appendix Table 1. Nationally projected sales distribution for the bisphosphonates approved for osteoporosis, by distribution channel

	2008		2009		2010	
	bottles or vials (000)	**Share**	**bottles or vials (000)**	**Share**	**bottles or vials (000)**	**Share**
	n	%	n	%	n	%
Total	23,826	100.0%	46,709	100.0%	40,187	100.0%
Alendronate	13,877	58.2%	30,888	66.1%	28,185	70.1%
Retail	8,766	63.2%	19,692	63.8%	18,757	66.5%
Non-retail	1,558	11.2%	4,528	14.7%	4,535	16.1%
Mail Service	3,553	25.6%	6,668	21.6%	4,894	17.4%
Risedronate	5,896	24.8%	9,498	20.3%	7,224	18.0%
Retail	4,241	71.9%	6,855	72.2%	5,338	73.9%
Non-retail	603	10.2%	907	9.5%	644	8.9%
Mail Service	1,053	17.8%	1,736	18.3%	1,241	17.2%
Alendronate w/ D	1,990	8.4%	2,180	4.7%	1,069	2.7%
Retail	1,145	57.5%	1,260	57.8%	584	54.7%
Non-retail	285	14.3%	232	10.6%	132	12.3%
Mail Service	561	28.2%	688	31.6%	353	33.0%
Ibandronic Acid*	1,447	6.1%	2,812	6.0%	2,375	5.9%
Retail	919	63.5%	1,701	60.5%	1,384	58.3%
Non-retail	130	9.0%	308	11.0%	315	13.3%
Mail Service	398	27.5%	802	28.5%	676	28.4%
Zoledronic Acid	533	2.2%	1,230	2.6%	1,326	3.3%
Retail	4	.8%	10	0.9%	10	0.8%
Non-retail	518	97.2%	1,196	97.3%	1,290	97.3%
Mail Service	10	2.0%	23	1.9%	25	1.9%
Risedronate/Calcium	83	0.4%	101	0.2%	8	0.0%
Retail	59	71.3%	69	68.1%	5	62.4%
Non-retail	2	3.0%	4	3.7%		3.7%
Mail Service	21	25.7%	28	28.1%	3	33.9%

*Includes oral and intravenous products

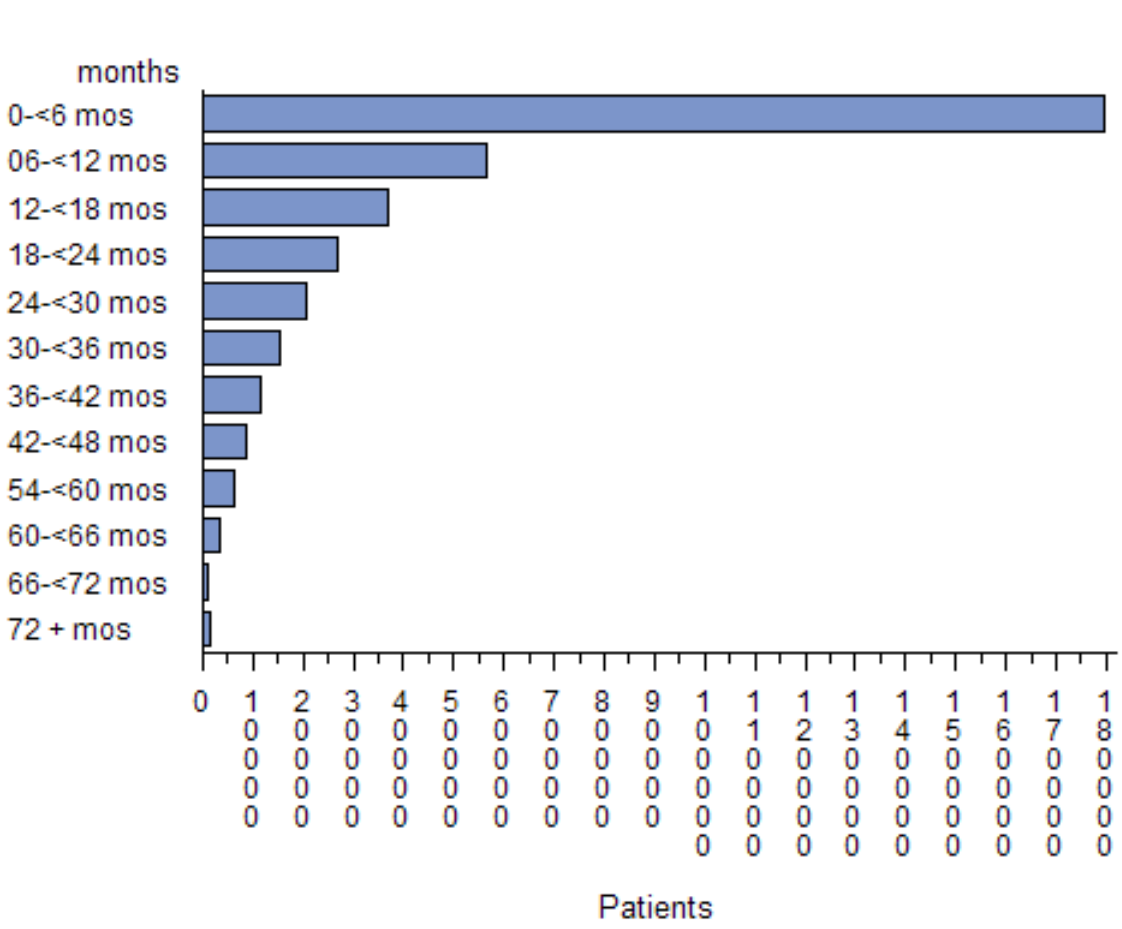
Source: IMS Health, National Sales PerspectivesTM, data extracted 8/5/2011 file:NSP BPA 8/2011.xls

Appendix Table 2. Summary of data cleaning procedures, SDI Vector One, 2006-2010

	Patients remaining	Percent of original dataset	Percent lost from previous step
Total patients dispensed bisphosphonates	7,482,896		
Limiting to stable pharmacies*	1,975,303		
Limiting to active patients*	919,932		
Initial analytic dataset	919,932	100.0%	
-Removal prevalent bisphosphonate users	533,379	58.0%	42.0%
-Removal of Patients less than 35 years of age	530,327	57.6%	0.6%
-Removal of patients receiving bisphosphonates approved for cancer or Paget's disease treatment	386,966	42.1%	27.0%
-Removal of patients with total days supply exceeding 6 years or high daily doses	369,156	40.1%	4.6%
-Patients remaining in final analysis dataset	369,156	40.1%	

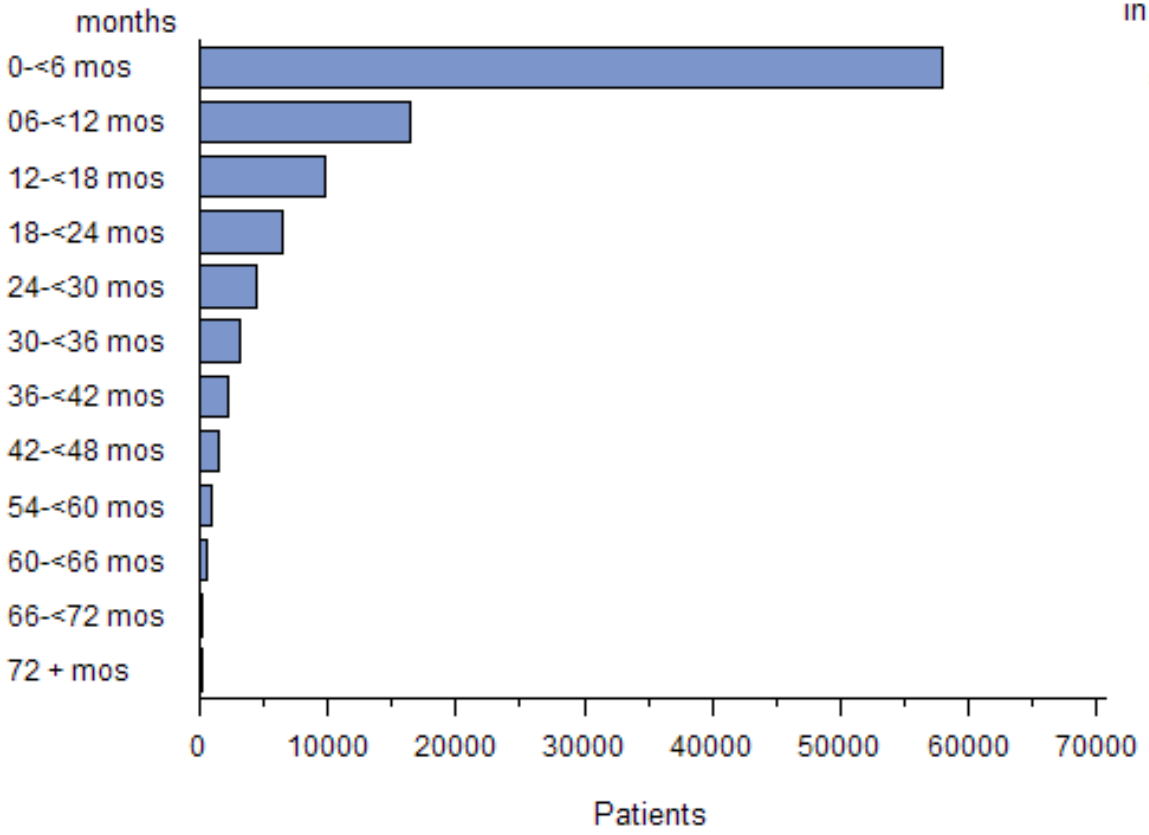
* limitations applied by SDI prior to dataset delivery (add definitions)

Appendix Figure 2. Total duration of therapy for patients receiving a bisphosphonate indicated for osteoporosis, **SDI Vector One, 2006-2010**



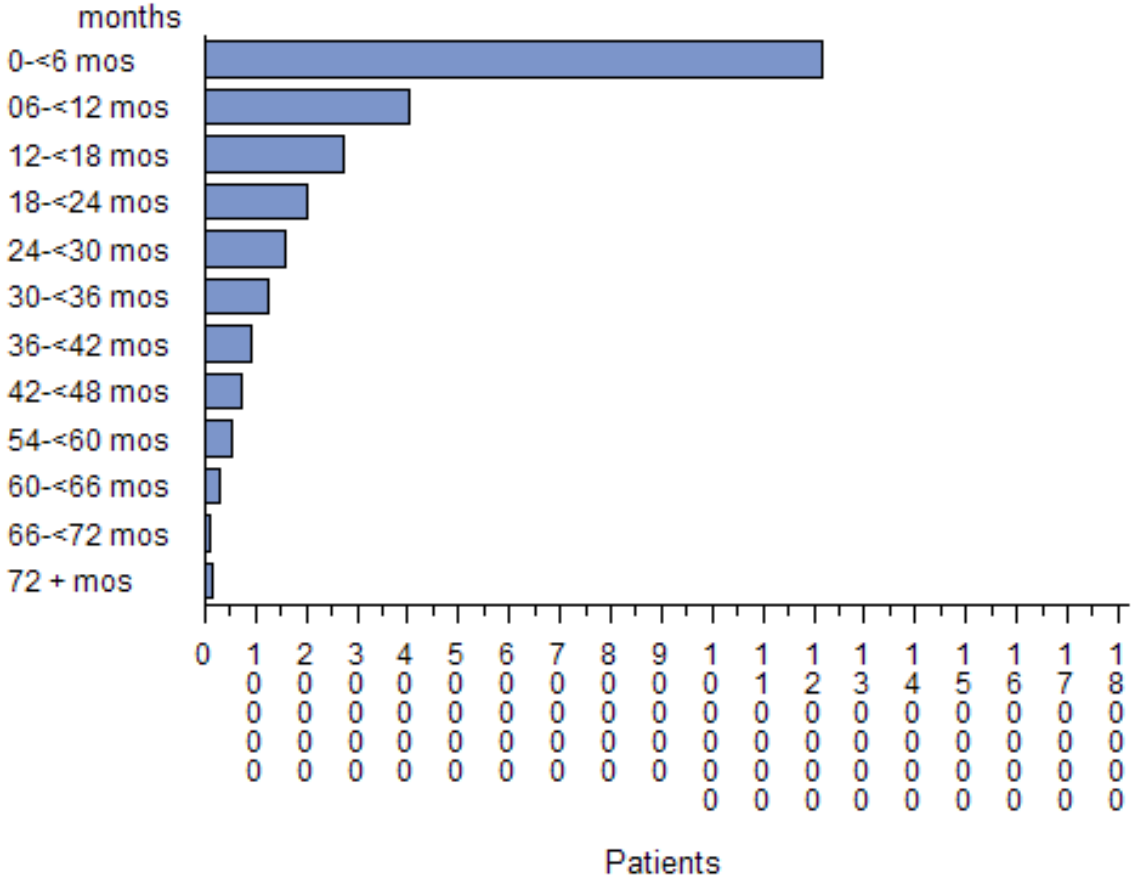
	Number in group	CUM. FREQ.	PCT.	CUM. PCT.
0-<6 mos	179782	179782	48.70	48.70
06-<12 mos	56613	236395	15.34	64.04
12-<18 mos	37134	273529	10.06	74.10
18-<24 mos	26685	300214	7.23	81.32
24-<30 mos	20406	320620	5.53	86.85
30-<36 mos	15588	336208	4.22	91.07
36-<42 mos	11538	347746	3.13	94.20
42-<48 mos	8879	356625	2.41	96.61
54-<60 mos	6236	362861	1.69	98.29
60-<66 mos	3592	366453	0.97	99.27
66-<72 mos	1032	367485	0.28	99.55
72 + mos	1671	369156	0.45	100.00

Appendix Figure 3. Total duration of use for patients receiving a bisphosphonate indicated for osteoporosis, with start of therapy at age 35-60 years, **SDI Vector One, 2006-2010**



months	Number in group	CUM. FREQ.	PCT.	CUM. PCT.
0-<6 mos	57983	57983	55.71	55.71
06-<12 mos	16508	74491	15.86	71.57
12-<18 mos	9801	84292	9.42	80.98
18-<24 mos	6507	90799	6.25	87.23
24-<30 mos	4477	95276	4.30	91.53
30-<36 mos	3233	98509	3.11	94.64
36-<42 mos	2172	100681	2.09	96.73
42-<48 mos	1545	102226	1.48	98.21
54-<60 mos	966	103192	0.93	99.14
60-<66 mos	509	103701	0.49	99.63
66-<72 mos	140	103841	0.13	99.76
72 + mos	246	104087	0.24	100.00

Appendix Figure 4. Total duration of use for patients receiving a bisphosphonate indicated for osteoporosis, with start of therapy at age > 60 years, **SDI Vector One, 2006-2010**



months	Number in group	CUM. FREQ.	PCT.	CUM. PCT.
0-<6 mos	121799	121799	45.95	45.95
06-<12 mos	40105	161904	15.13	61.08
12-<18 mos	27333	189237	10.31	71.39
18-<24 mos	20178	209415	7.61	79.00
24-<30 mos	15929	225344	6.01	85.01
30-<36 mos	12355	237699	4.66	89.67
36-<42 mos	9366	247065	3.53	93.21
42-<48 mos	7334	254399	2.77	95.97
54-<60 mos	5270	259669	1.99	97.96
60-<66 mos	3083	262752	1.16	99.13
66-<72 mos	892	263644	0.34	99.46
72 + mos	1425	265069	0.54	100.00

Appendix Table 3. Pay type at initial prescription, by duration of therapy* SDI Vector One, 2006-2010

	< 5 years therapy		> 5 years therapy	
	n	%	n	%
Third Party	214,170	58.5	1,219	44.4
Medicare	135,611	37.0	1,444	52.6
Cash	16,632	4.5	80	2.92

*For patients receiving bisphosphonates indicated for osteoporosis only

Appendix Table 4. Physician specialty at initial prescription, by duration of therapy* SDI Vector One, 2006-2010

	< 5 years therapy		> 5 years therapy	
	n	%	n	%
Internal Medicine	122,833	34.6	1,008	37.7
Family Practice	121,122	34.1	889	33.2
Obstetrics & Gynecology	32,533	9.2	259	9.7
Rheumatology	16,557	4.7	98	3.7
Endocrine, Diabetes & Metabolic	7,591	2.1	60	2.2
General Practice	5,338	1.5	45	1.7
Gynecology	4,375	1.2	32	1.2
Medical Oncology	3,226	0.9	18	0.7
Cardiovascular Disease	3,068	0.9	28	1.0
Orthopedic Surgery	3,026	0.9	8	0.3
Other	35,058	9.9	230	8.6

* For patients receiving bisphosphonates indicated for osteoporosis only

Appendix Table 5. Drug product at initial prescription, by duration of therapy*, SDI Vector One, 2006-2010

	< 5 years therapy		> 5 years therapy	
	n	%	n	%
Total	366,413		2,743	
Alendronate 70 Mg	135,442	37.0	157	5.7
Fosamax 70 Mg	94,353	25.8	1,650	60.2
Boniva 150 Mg	84,548	23.1	391	14.3
Fosamax P 70-2800 Mg	25,457	6.9	311	11.3
Alendronate 35 Mg	11,060	3.0	17	0.6
Fosamax 35 Mg	9,137	2.5	154	5.6
Fosamax P 70-5600 Mg	2,383	0.7	14	0.5
Fosamax 10 Mg	1,515	0.4	39	1.4
Alendronate 10 Mg	1,170	0.3	0	0.0
Fosamax 5 Mg	327	0.1	7	0.3
Alendronate 5 Mg	313	0.1	1	0.0
Boniva 3 Mg/3 Ml	266	0.1	0	0.0
Reclast 5 Mg/100 Ml	240	0.1	0	0.0
Boniva 2.5 Mg	76	0.0	0	0.0
Fosamax 70 Mg/75 Ml	61	0.0	1	0.0
Alendronate 40 Mg	43	0.0	0	0.0
Fosamax 40 Mg	21	0.0	1	0.0
Atelvia 35 Mg	1	0.0	0	0.0

* For patients receiving bisphosphonates indicated for osteoporosis only

Appendix Table 6. Drug product at final prescription, by duration of therapy*, SDI Vector One, 2006-2010

	< 5 years therapy		> 5 years therapy	
	n	%	n	%
Total	366,413		2,743	
Alendronate 70 Mg	199,914	54.6	2,015	73.5
Boniva 150 Mg	84,727	23.1	397	14.5
Fosamax 70 Mg	39,669	10.8	32	1.2
Fosamax P 70-2800 Mg	16,929	4.6	87	3.2
Alendronate 35 Mg	15,016	4.1	144	5.2
Fosamax 35 Mg	4,184	1.1	3	0.1
Fosamax P 70-5600 Mg	2,505	0.7	38	1.4
Alendronate 10 Mg	1,541	0.4	19	0.7
Fosamax 10 Mg	675	0.2	1	0.0
Alendronate 5 Mg	362	0.1	3	0.1
Boniva 3 Mg/3 Ml	316	0.1	2	0.1
Reclast 5 Mg/100 Ml	309	0.1	1	0.0
Fosamax 5 Mg	158	0.0	0	0.0
Alendronate 40 Mg	48	0.0	1	0.0
Boniva 2.5 Mg	39	0.0	0	0.0
Fosamax 70 Mg/75 Ml	15	0.0	0	0.0
Fosamax 40 Mg	5	0.0	0	0.0
Atelvia 35 Mg	1	0.0	0	0.0

* For patients receiving bisphosphonates indicated for osteoporosis only

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